Pharmacia

Therapy of Colorectal Cancer with Combination Regimens of CAMPTOSAR® (Irinotecan, CPT-11), 5-Fluorouracil (5-FU), and Leucovorin (LV)

Oncologic Drugs Advisory Committee Review
December 6, 2001

April 2000

First-line CPT-11/5-FU/LV for Metastatic Colorectal Cancer

- Received FDA approval
- Demonstrated significant survival benefits over 5-FU/LV alone in 2 well-controlled phase III trials

April 2001

First-line CPT-11/5-FU/LV for Metastatic Colorectal Cancer

- Widespread adoption in community practice without safety problems
- Concerns regarding early mortality with CPT-11/bolus 5-FU/LV regimen in cooperative group trial (N9741)
- ***Apparent*** increase in early mortality due to comparison of 2 dissimilar mortality rates

Presentation Agenda

- Summarize background and registration data
- Describe mortality concerns raised in cooperative group studies
- Place mortality concerns into context
- Describe rationale for Pharmacia proposals to strengthen CAMPTOSAR package insert for metastatic colorectal cancer

Presentation Summary

Bolus and Infusional CPT-11/5-FU/LV for Metastatic Colorectal Cancer

- Provide statistically significant tumor control and survival benefits relative to 5-FU/LV alone
- Have *NO* greater mortality risk than 5-FU/LV alone
- Both regimens should be retained in the CAMPTOSAR package insert

Background

Pre-April 2000

5-FU for Metastatic Colorectal Cancer

- Thymidylate synthase inhibitor
- Mainstay of therapy for 40 years
- Commonly given with potentiating agent, leucovorin (LV)

5-FU/LV Regimens

United States	Europe
Bolus **Regimens**	***Infusional*** **Regimens**
Monthly (Mayo Clinic)*	Biweekly (de Gramont)‡
Weekly (Roswell Park)†	Weekly (AIO)§

*Poon *et al. J Clin Oncol* 7:1407, 1989.
†Petrelli *et al. J Clin Oncol* 7:1419, 1989.
‡de Gramont *et al. J Clin Oncol* 15:808, 1997.
§Köhne *et al. J Clin Oncol* 16:418, 1998.

5-FU/LV Regimens

United States	Europe
Bolus **Regimens**	***Infusional*** **Regimens**
Monthly (Mayo Clinic) Weekly (Roswell Park)	Biweekly (de Gramont) Weekly (AIO)

- **Response rates remained at 20-25%**
- **Median survival was only 11-12 months**

Meta-analysis Group in Cancer. *J Clin Oncol* 10:896, 1992.
Meta-analysis Group in Cancer. *J Clin Oncol* 16:301, 1998.

CPT-11 Therapy of Colorectal Cancer

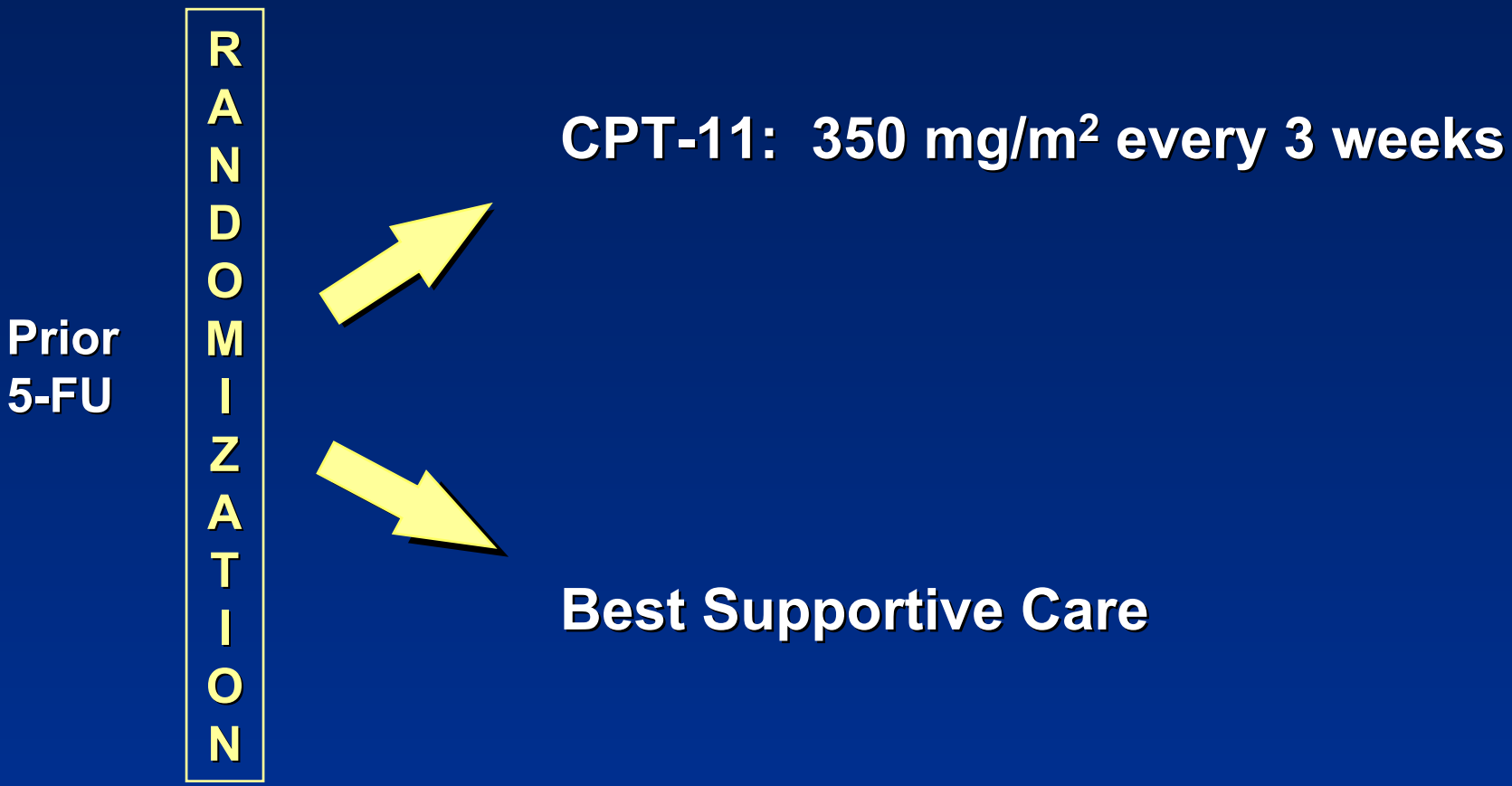
What was needed?

- A novel agent with a different mechanism of action

CPT-11 offered

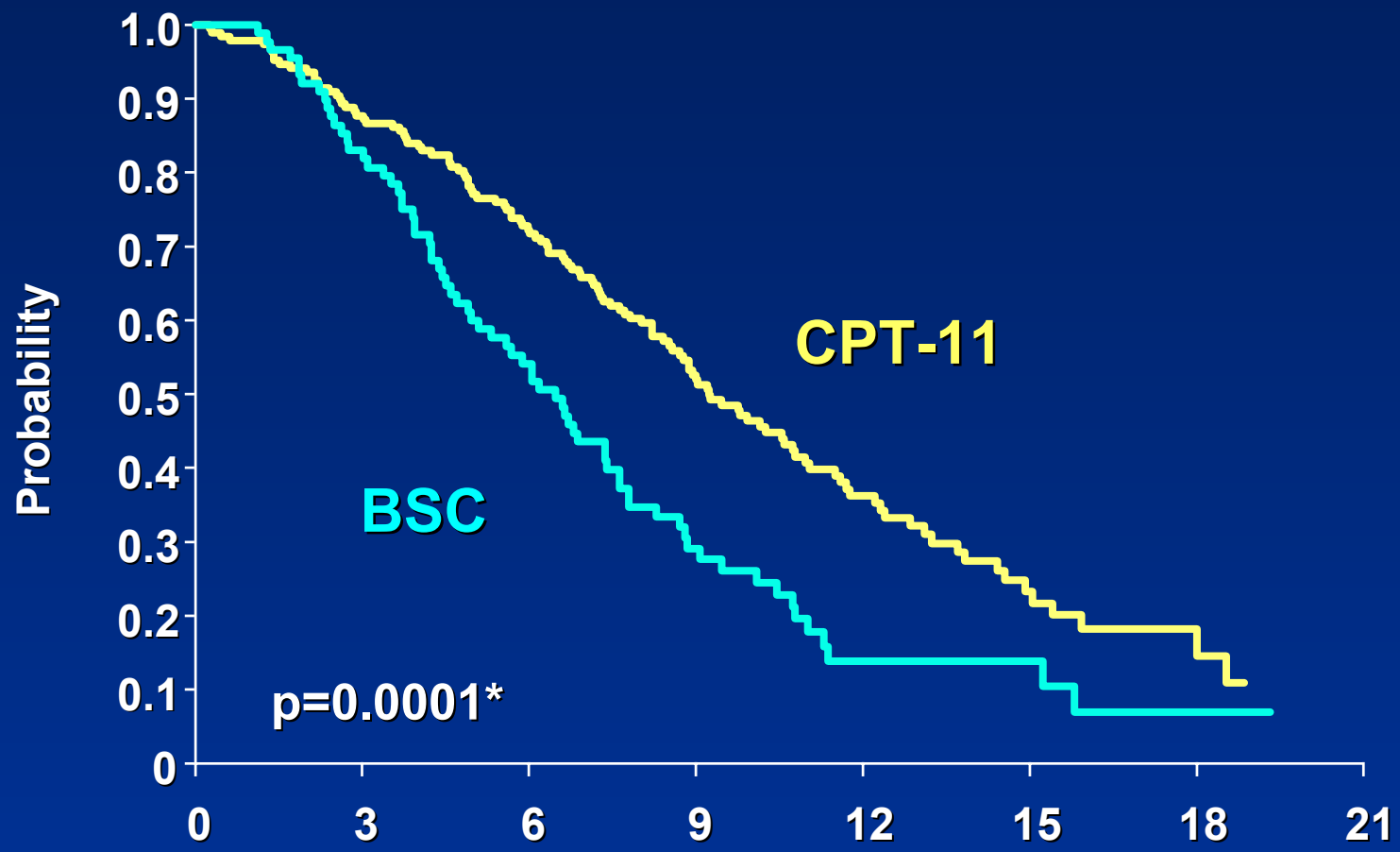
- Topoisomerase I inhibition
- Consistent activity in colorectal cancer

Second-Line CPT-11 Therapy (Study V301)



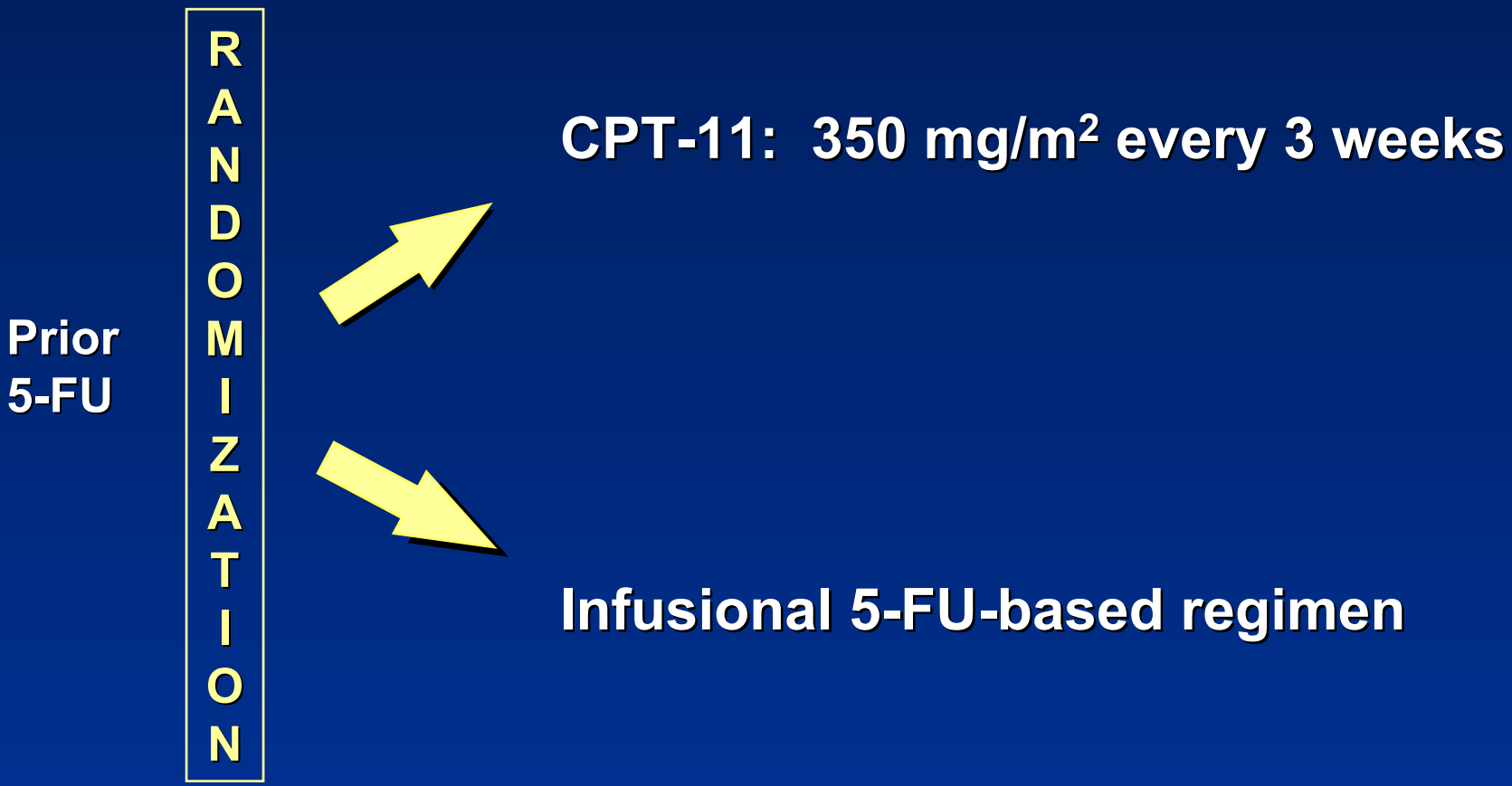
Cunningham *et al.* *Lancet* 352:1413, 1998.

Second-Line Survival
(Study V301)



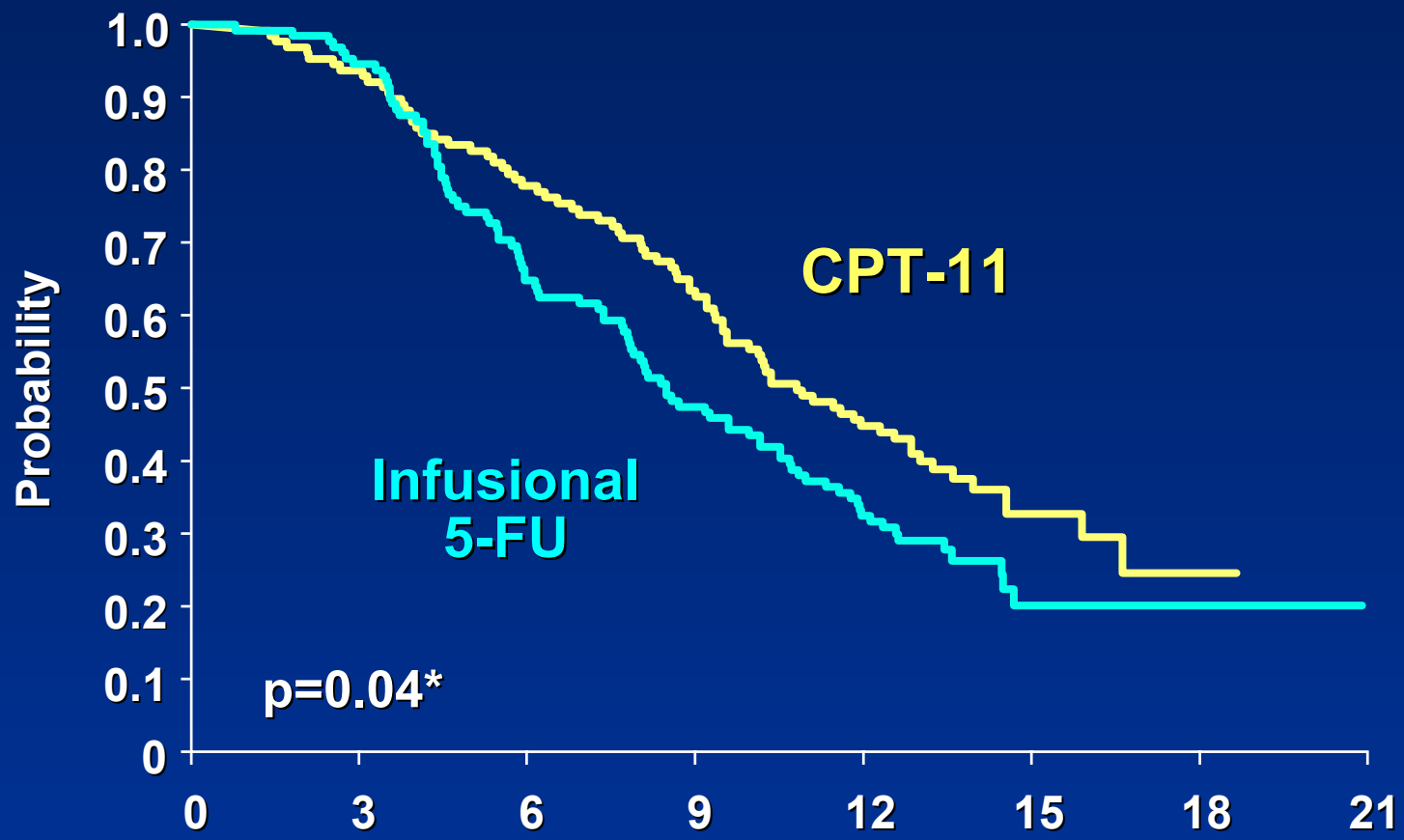
*log-rank test

Second-Line CPT-11 Therapy
(Study V302)



Rougier *et al.* *Lancet* 352:1407, 1998.

Second-Line Survival
(Study V302)



*log-rank test

CPT-11/5-FU/LV Registration as First-Line Therapy of Metastatic Colorectal Cancer

Well Controlled, Phase III Registration Trials

Two independent, phase III, prospective, randomized, controlled, international studies

Pharmacia Study 0038	Aventis Study V303
CPT-11/Bolus 5-FU/LV vs Bolus 5-FU/LV	CPT-11/Infusional 5-FU/LV vs Infusional 5-FU/LV

Treatment Arms
(Study 0038)

RANDOMIZATION

CPT-11: 125 mg/m^2/wk x 4 wks, q 6 wks
5FU: 500 mg/m^2/wk x 4 wks, q 6 wks
LV: 20 mg/m^2/wk x 4 wks, q 6 wks

Saltz Regimen

5FU: 425 mg/m^2/d x 5 d, q 4 wks
LV: 20 mg/m^2/d x 5 d, q 4 wks

Mayo Clinic Regimen

CPT-11: 125 mg/m^2/wk x 4 wks, q 6 wks

Saltz *et al. N Engl J Med* 343:905, 2000.

Treatment Arms
(Study V303)

RANDOMIZATION

CPT-11: 80 mg/m²/wk x 6 wks, q 7 wks
5-FU: 2.3 gm/m²/wk x 6 wks, q 7 wks
LV: 500 mg/m²/wk x 6 wks, q 7 wks
or
CPT-11: 180 mg/m² d1 q 2 wks
5-FU: 400 IV/600 CI mg/m² d1, 2 q 2 wks
LV: 200 mg/m² d1, 2 q 2 wks

AIO

Douillard

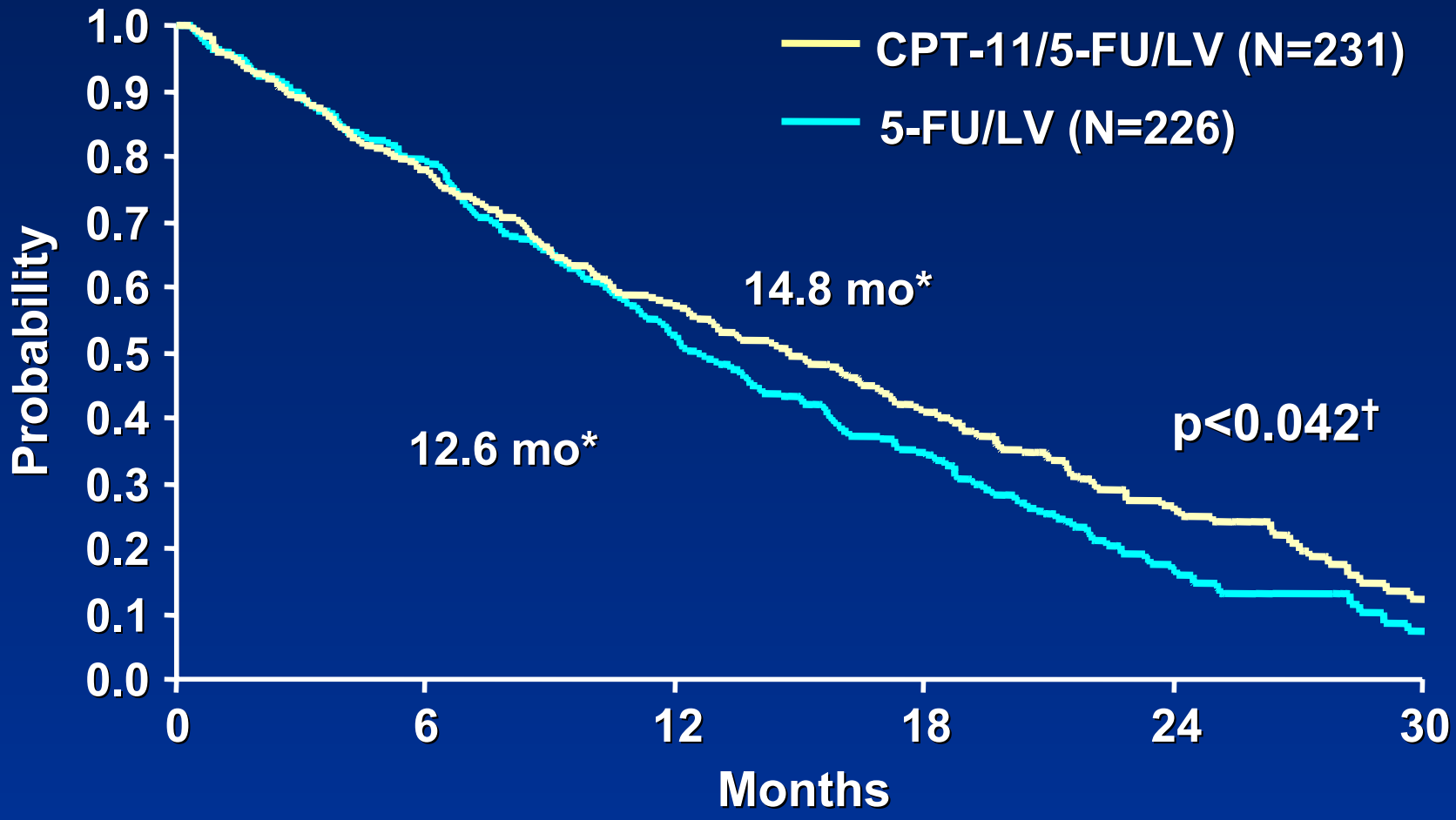
5-FU: 2.6 gm/m²/wk x 6 wks, q 7 wks
LV: 500 mg/m²/wk x 6 wks, q 7 wks
or
5-FU: 400 IV/600 CI mg/m² d1, 2 q 2 wks
LV: 200 mg/m² d1, 2 q 2 wks

AIO

de Gramont

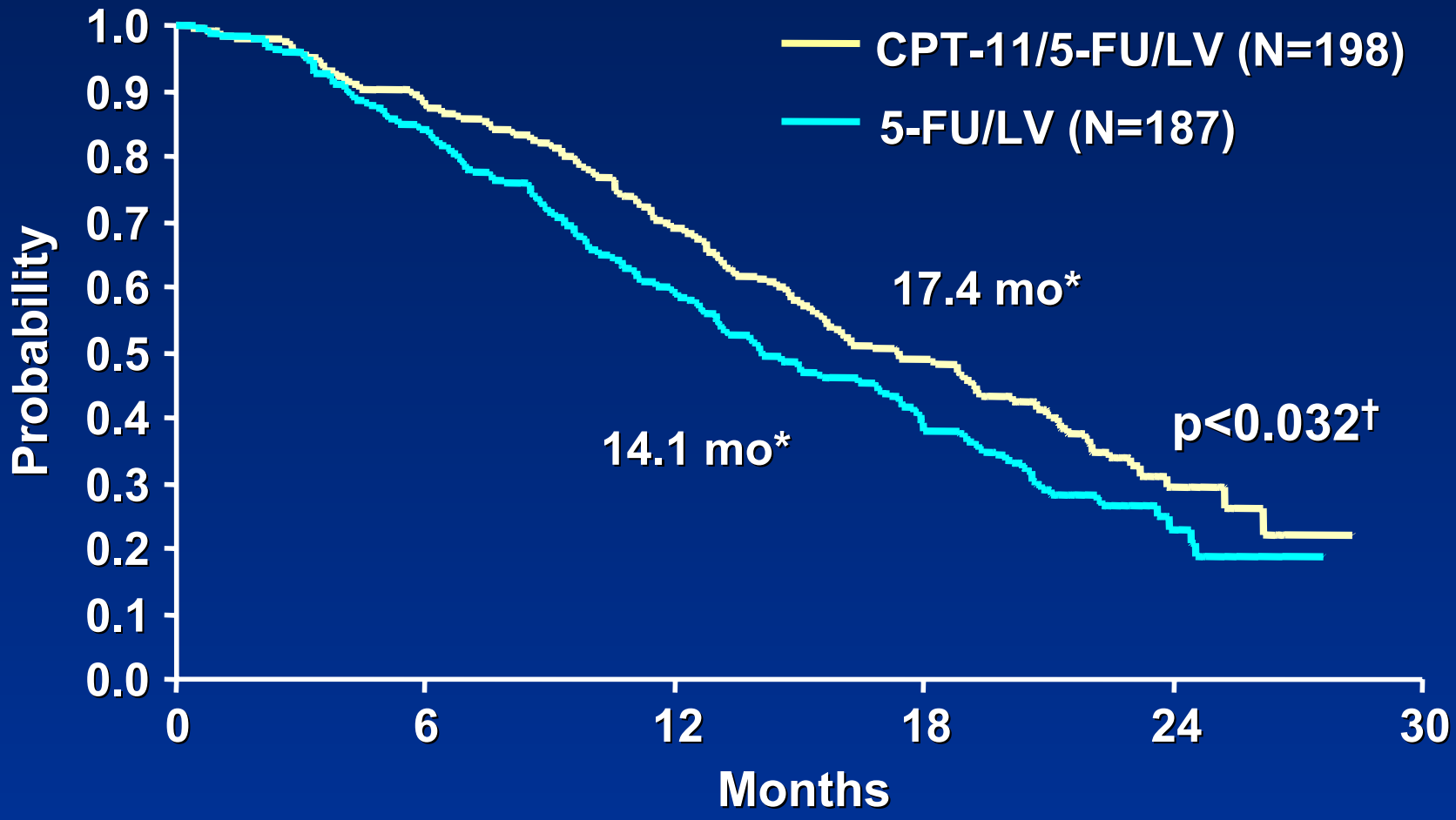
Douillard *et al*. *Lancet* 355:1041, 2000

Survival
(Study 0038)



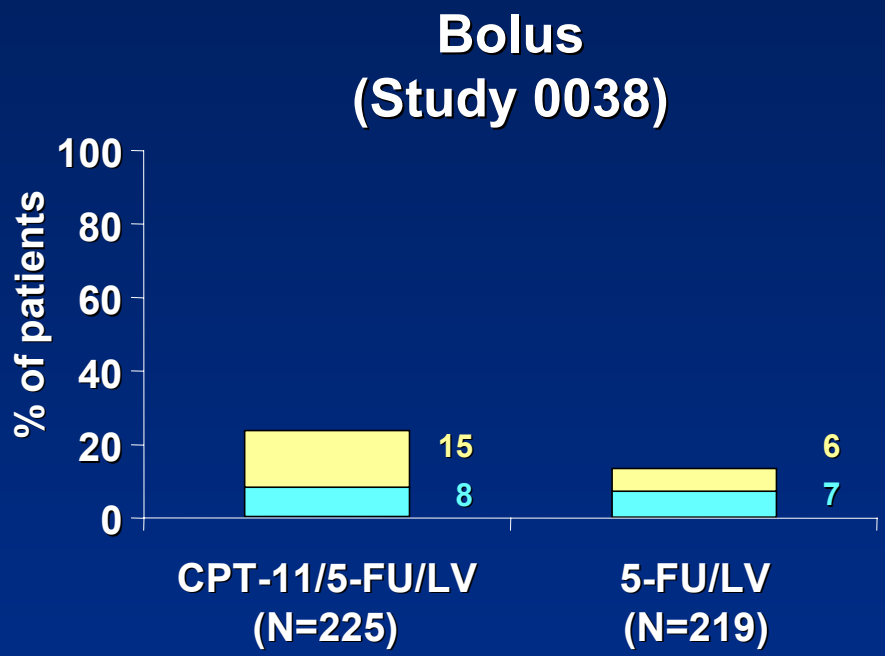
* Medians
† Log-rank test

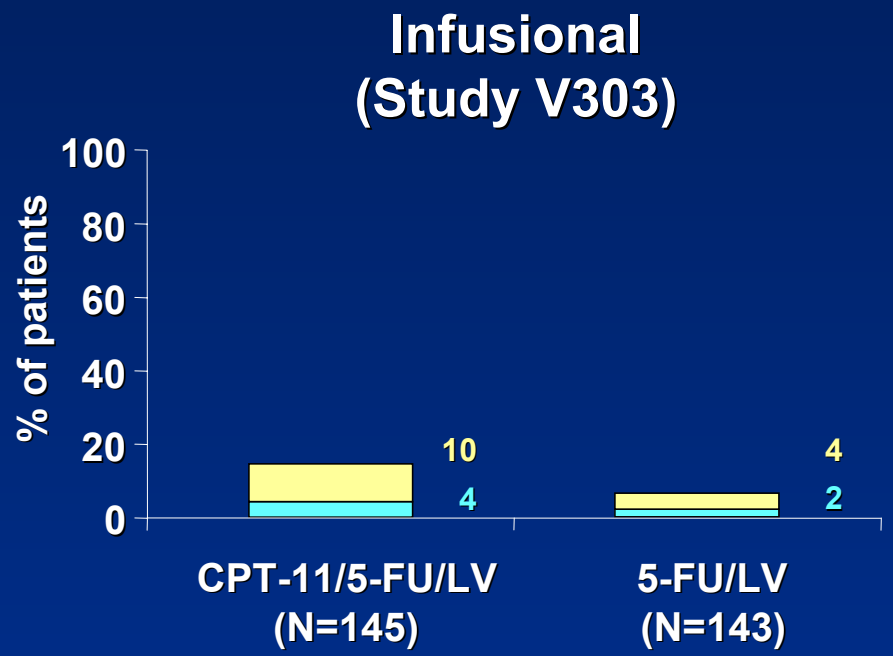
Survival
(Study V303)

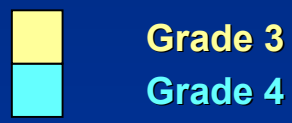


* Medians
† Log-rank test

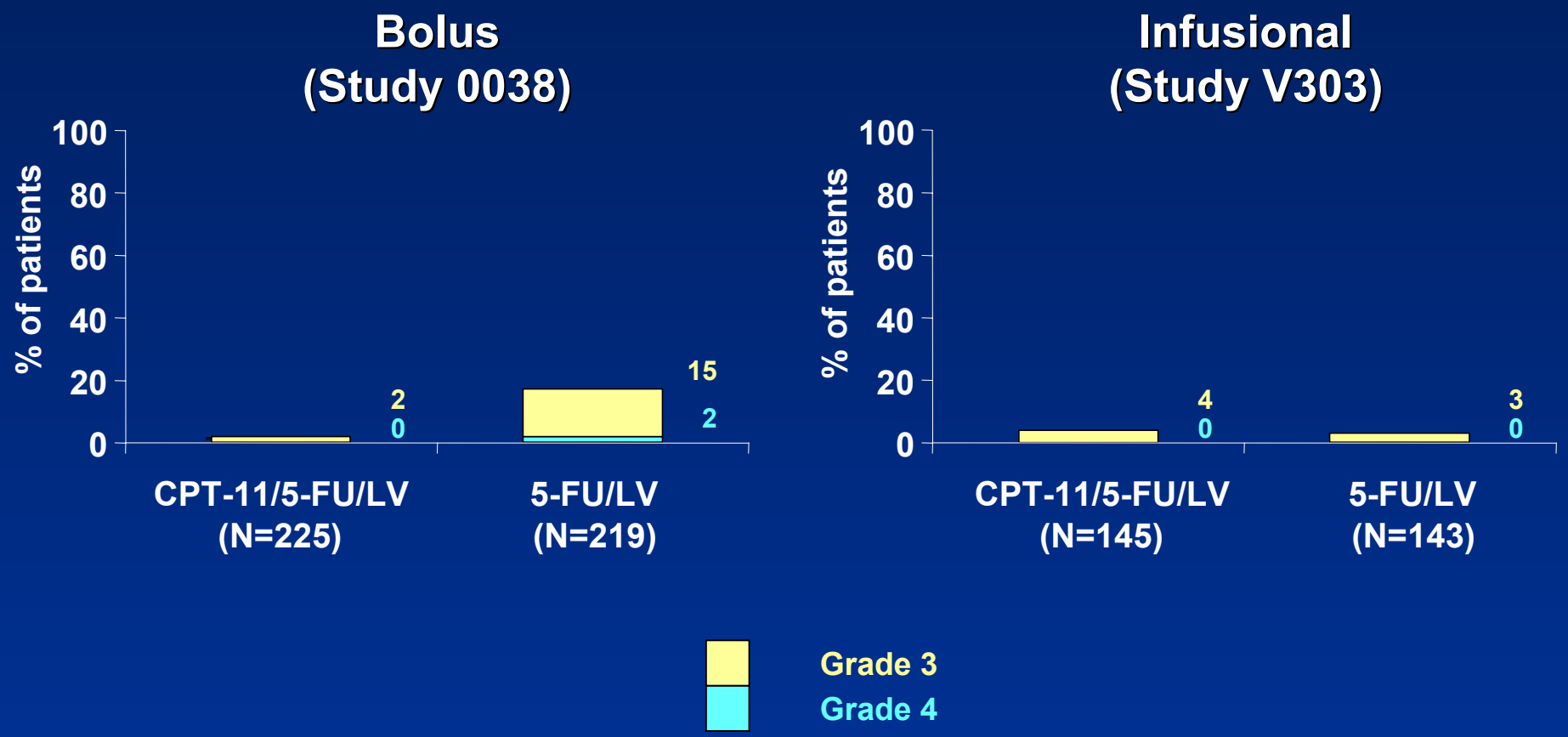
Grade 3-4 Diarrhea
(Studies 0038 and V303)



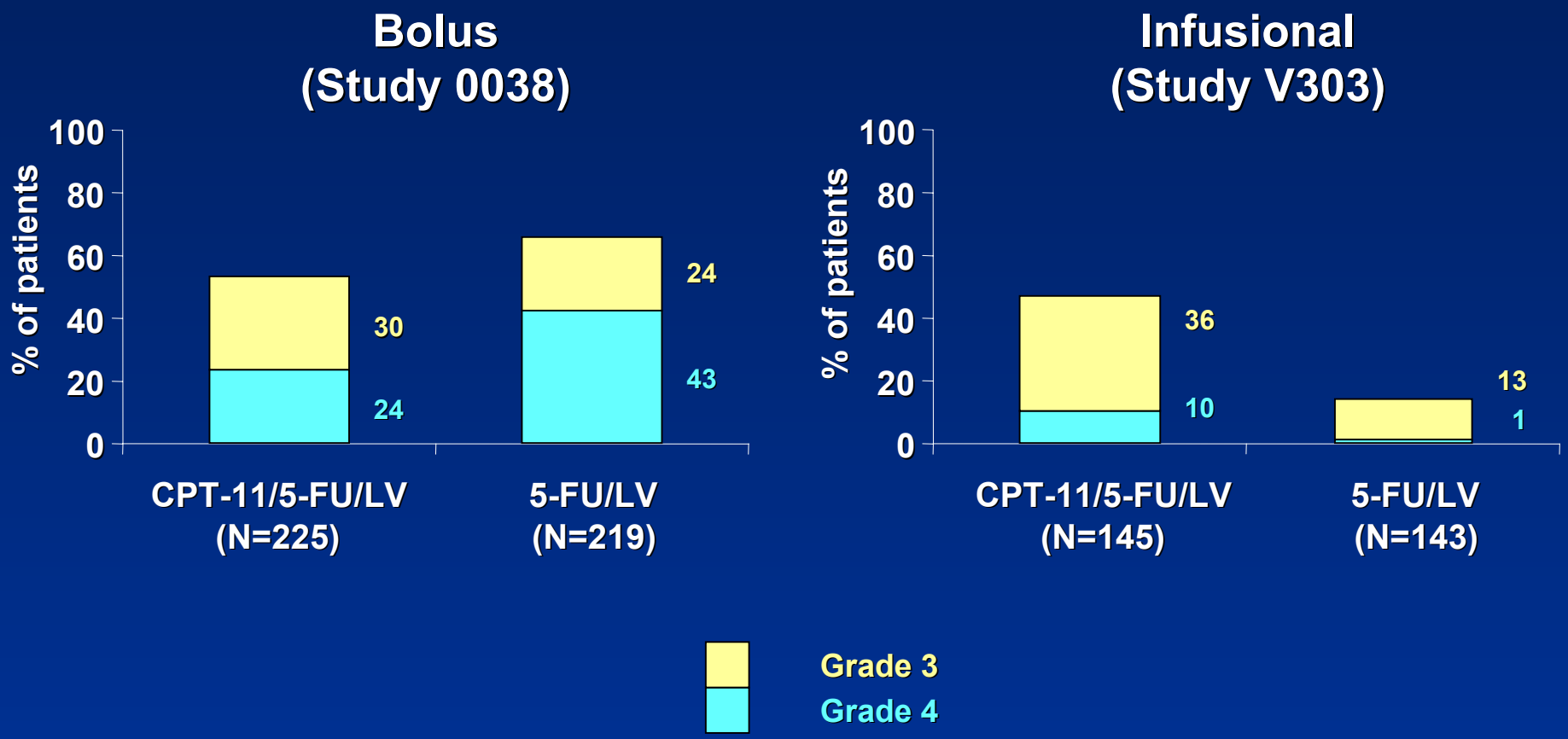




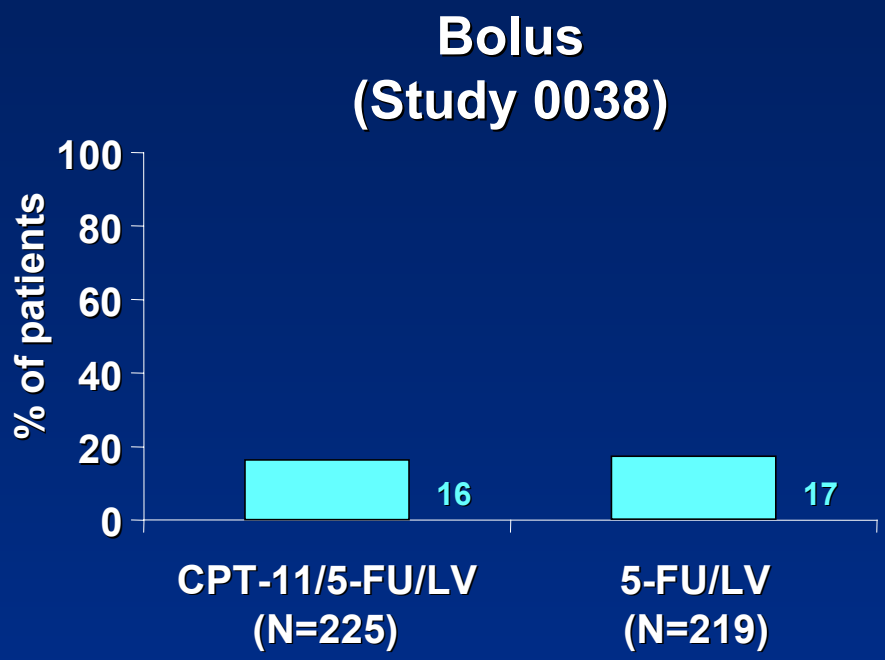
Grade 3-4 Mucositis
(Studies 0038 and V303)

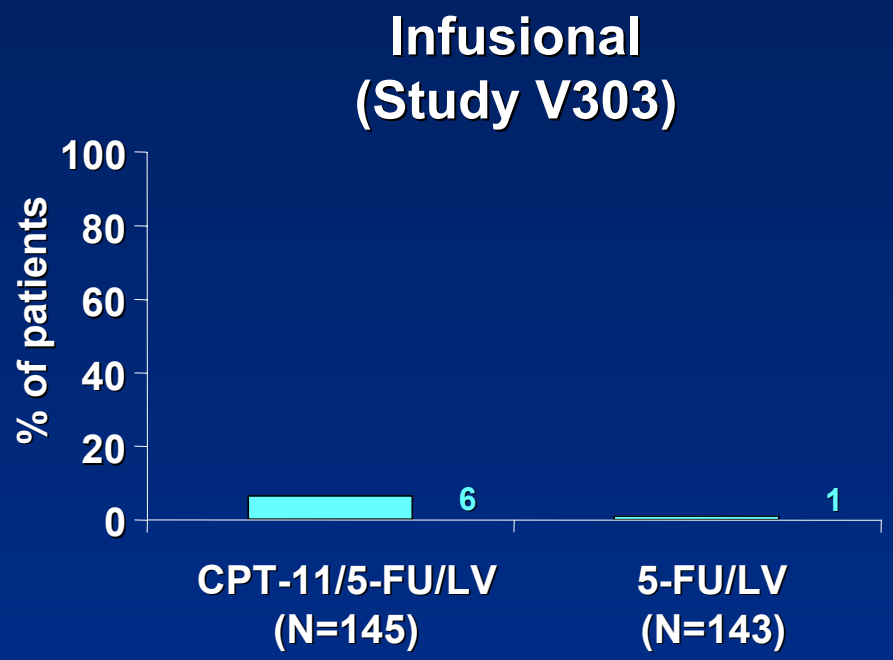


Grade 3-4 Neutropenia
(Studies 0038 and V303)



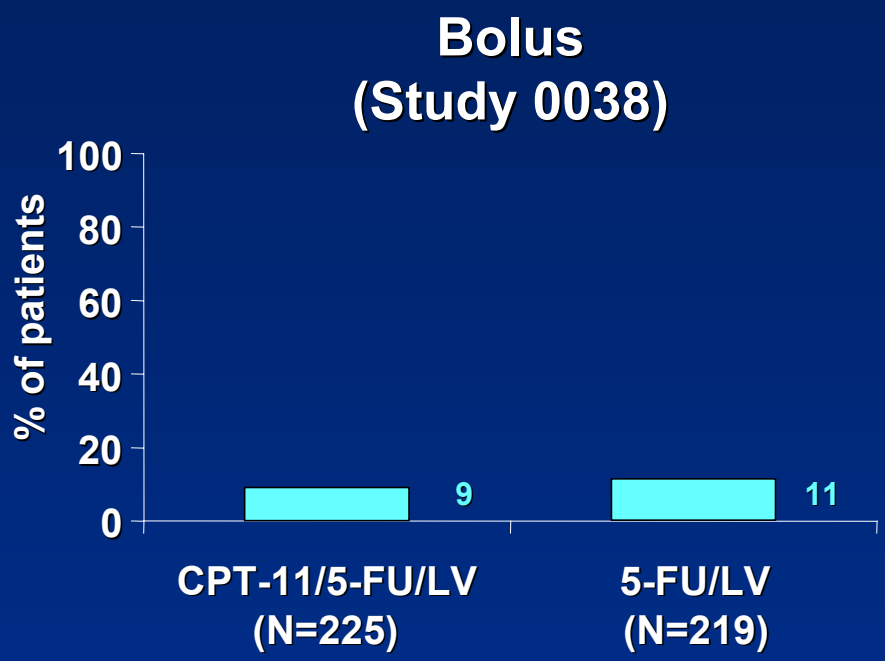
Neutropenic Fever/Infection*
(Studies 0038 and V303)

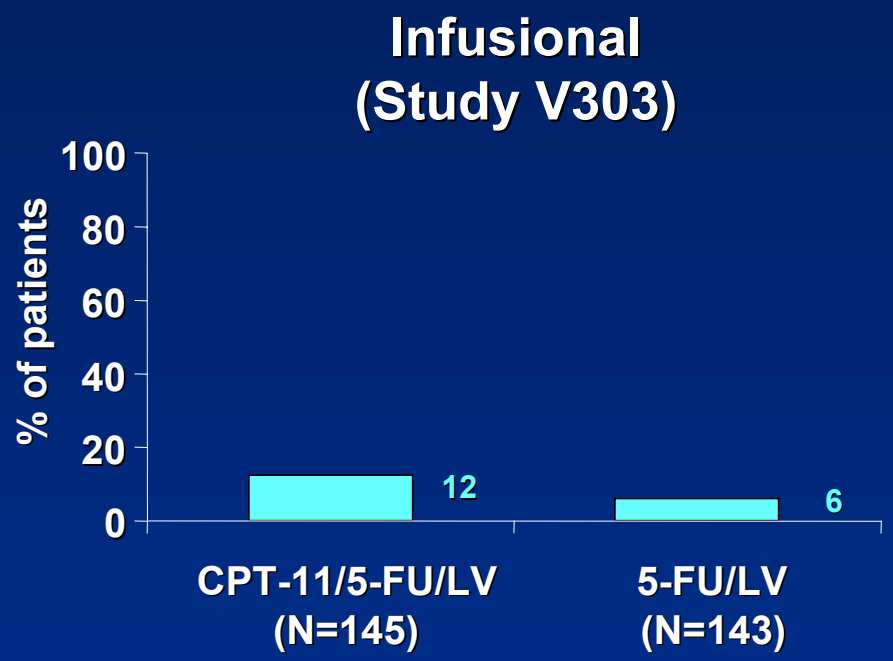




*Grade 3-4 neutropenia with grade 2 fever or grade 3-4 infection

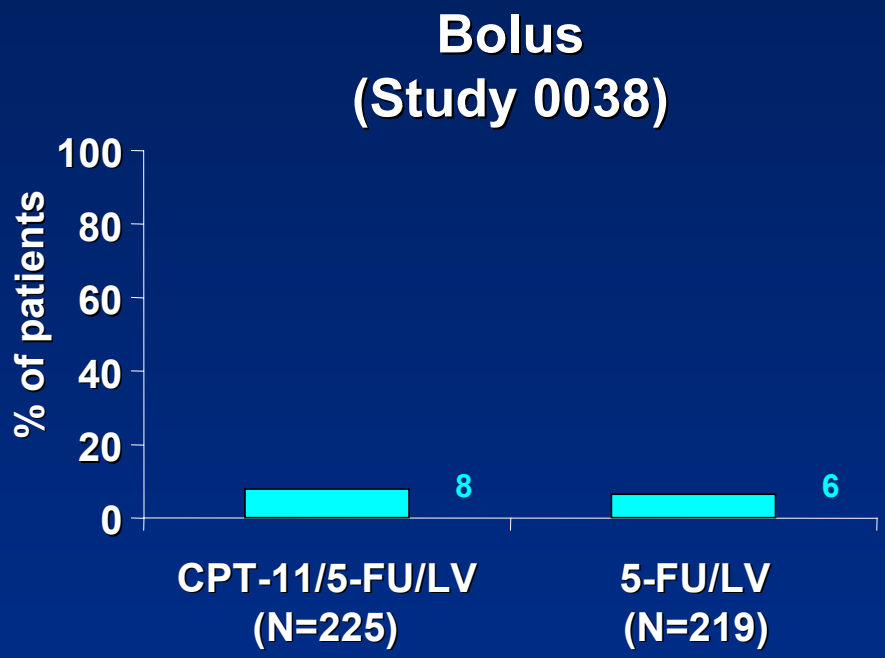
Thromboembolism
(Studies 0038 and V303)

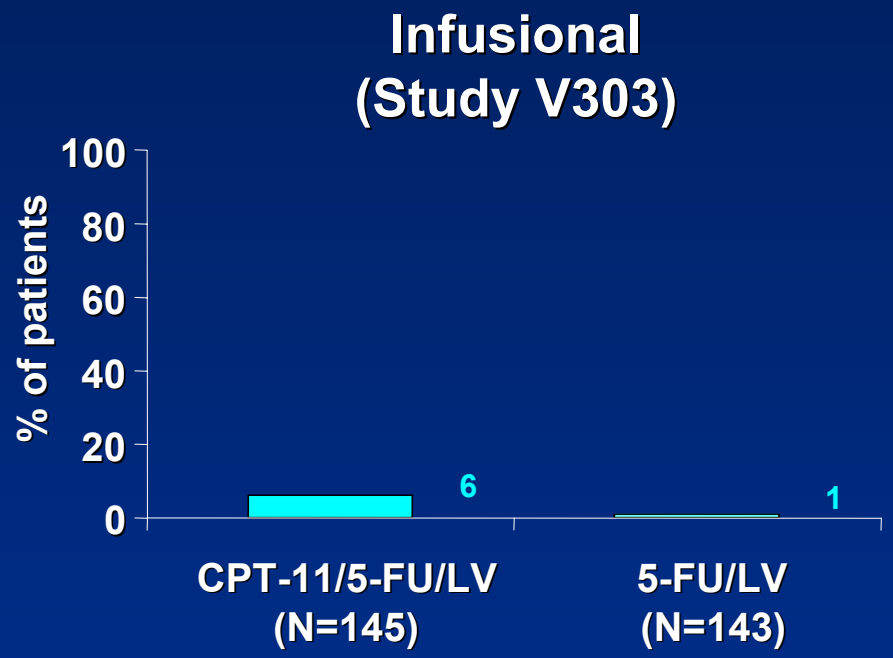




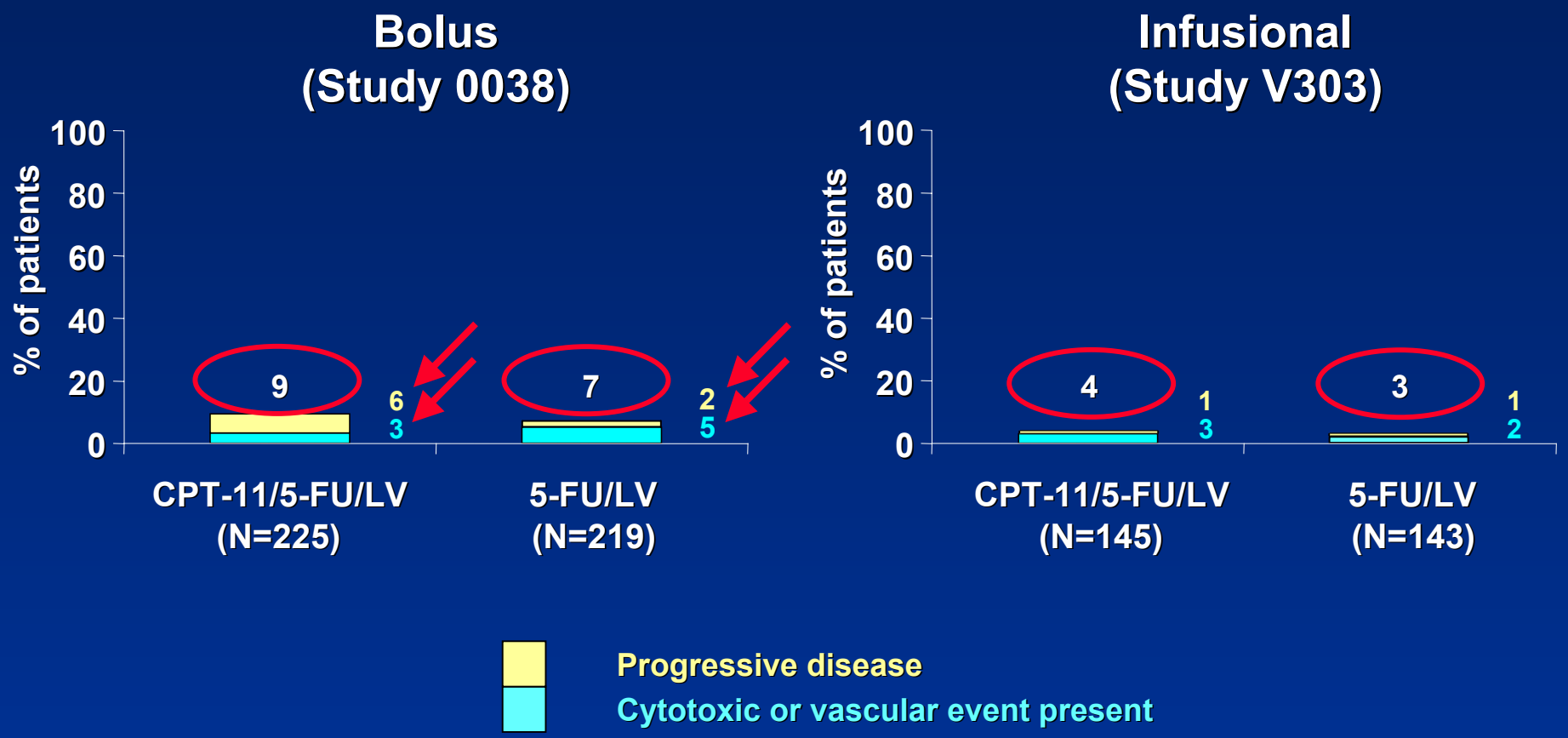
All grades

Discontinuations due to Adverse Events (Studies 0038 and V303)

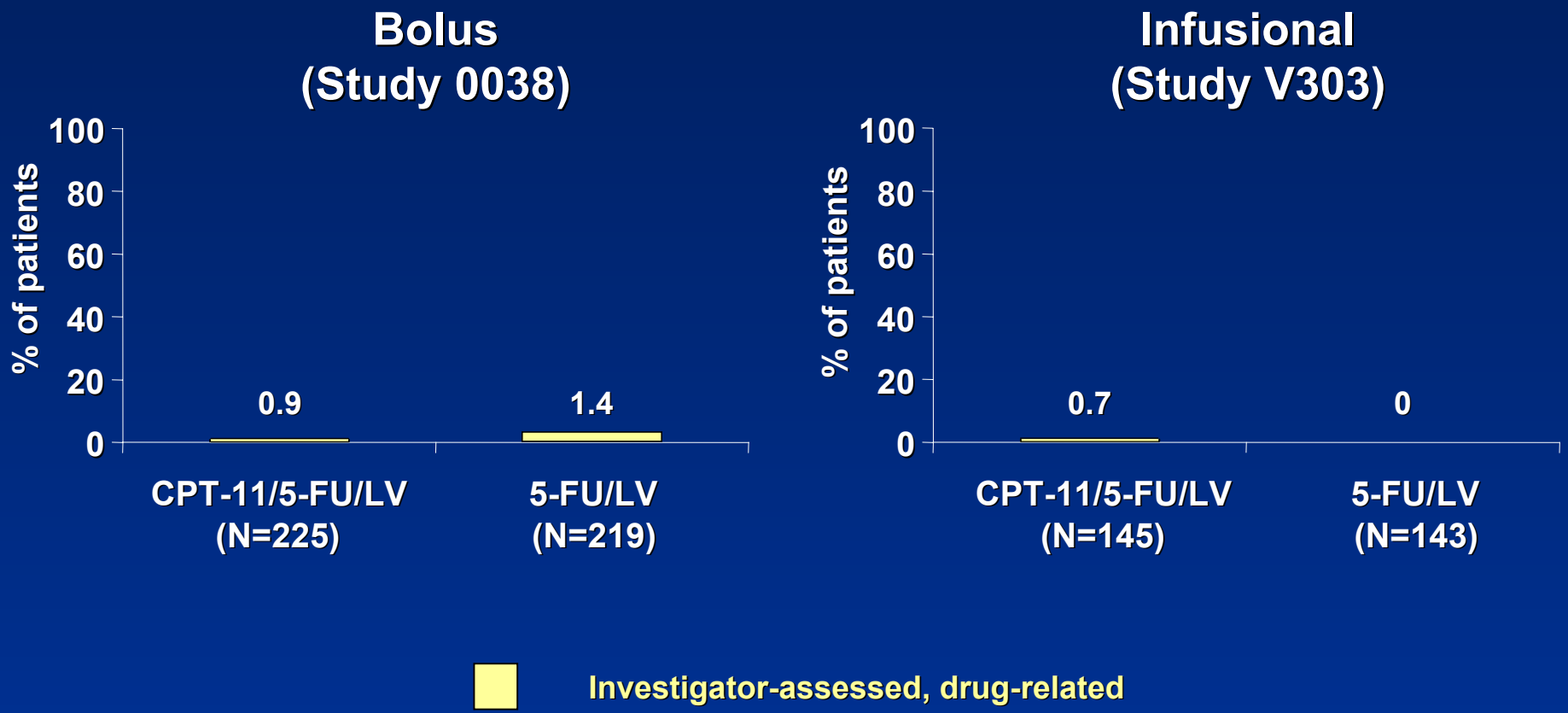




Deaths within 30 Days of End of Therapy (Studies 0038 and V303)



Investigator-Assessed, Drug-Related Deaths (Studies 0038 and V303)



Baseline Patient Characteristics
(Saltz and Douillard Regimens)

	CPT-11/5-FU/LV	
	Study 0038 N=225	Study V303 N=145
Age range, years	25-85	27-74
Performance status, %		
0	39	47
1 47	45	
2	15	8
Laboratory abnormalities, %		
LDH >ULN	60	41
Hemoglobin <11 g/dL	26	17

*ULN = upper limit of normal

Well Controlled Phase III Registration Studies

CPT-11/5-FU/LV
(Bolus and Infusional Regimens)

- Significantly improved survival over 5-FU/LV
- Safety profiles documented relative to widely used reference standards
- No increase in risk of toxic death over control patients receiving 5-FU/LV alone
- Relative safety cannot be established based on cross-study comparisons

ODAC 2000 Recommendation

CPT-11/5-FU/LV
(Bolus and Infusional Regimens)

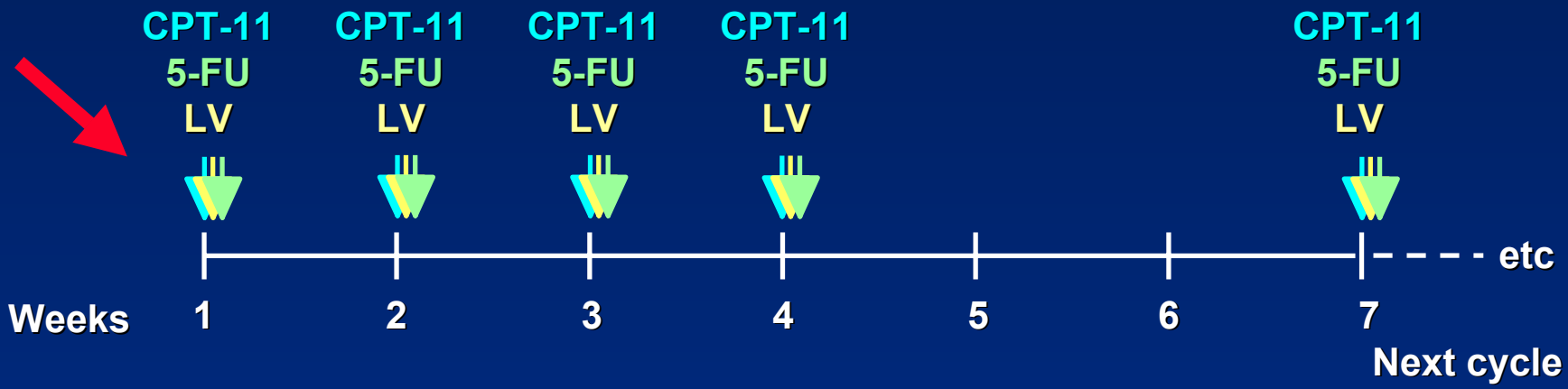
- Represents a new survival standard in the first-line treatment of metastatic colorectal cancer

Approved Indication

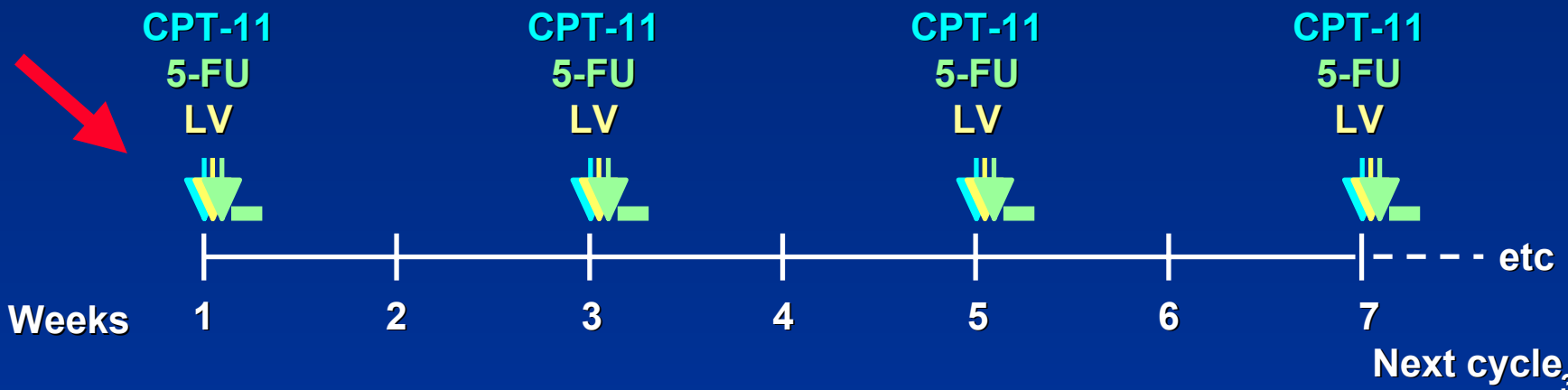
- CPT-11 indicated as a component of first-line therapy in combination with 5-FU/LV for patients with metastatic carcinoma of the colon or rectum
- Recommended CPT-11/5-FU/LV regimens:
  - Saltz weekly bolus
  - Douillard biweekly infusional

Recommended Regimens

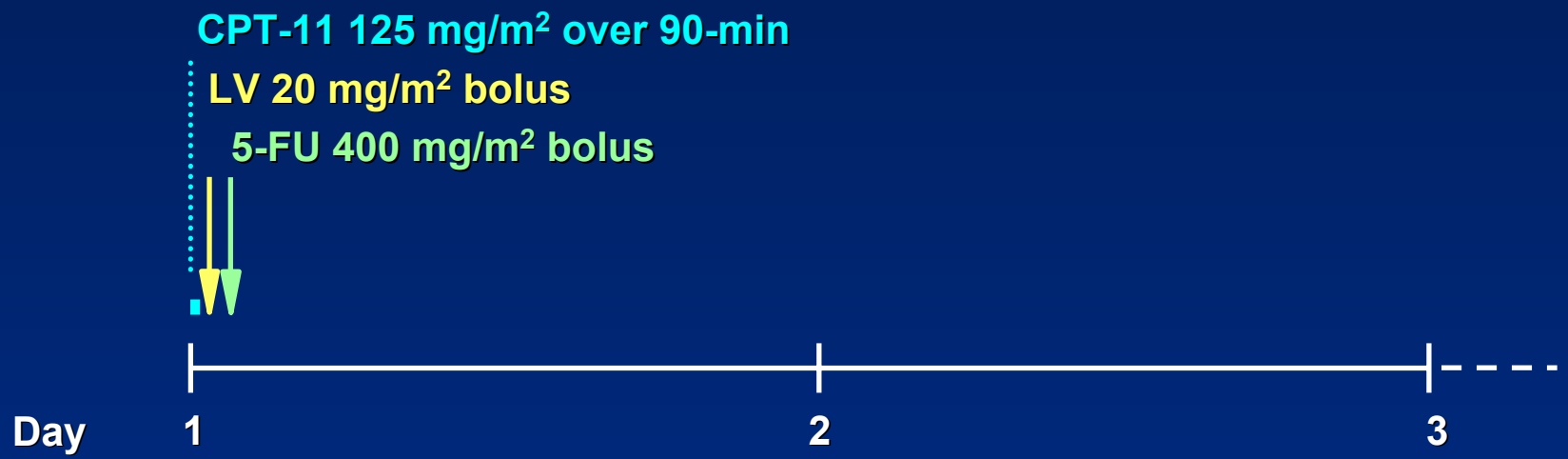
Weekly Bolus Regimen (Saltz)



Biweekly Infusional Regimen (Douillard)

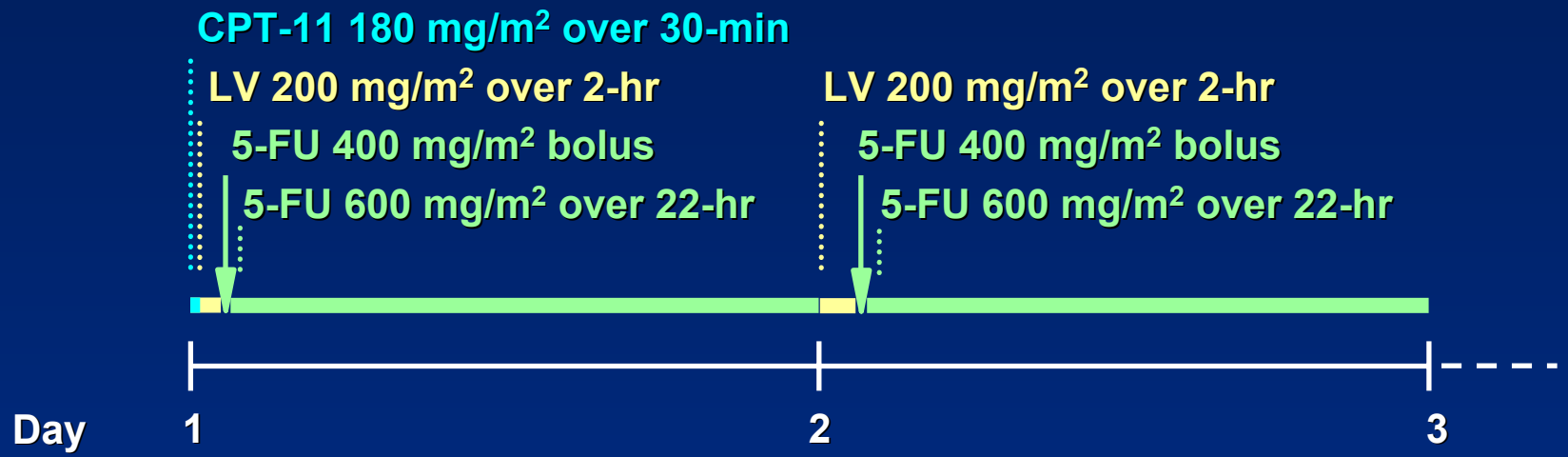


Starting Doses and Administration
(Weekly Bolus Regimen -- Saltz)



- Relatively simple
- Minimal patient and practitioner time
- Peripheral venous administration

Starting Doses and Administration
(Biweekly Infusional Regimen -- Douillard)



- More complex
- Greater patient and practitioner time commitment
- Requires central catheter & infusion pump

US Post-Approval Experience

US Post-Approval CPT-11/5-FU/LV Experience

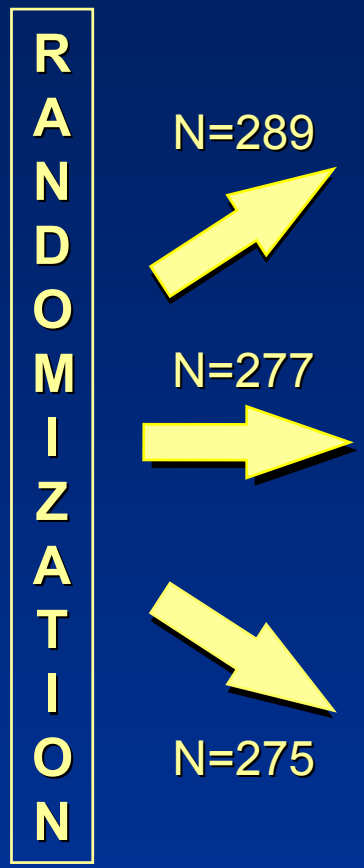
- First-line standard of care
  - Approximately 60% of patients receive CPT-11/5-FU/LV
  - 24,000 patients treated since approval
  - >95% receive weekly CPT-11/5-FU/LV bolus regimen
- Post-approval surveillance data since approval
  - 7 spontaneous reports of adverse events with fatal outcomes

Widespread adoption of bolus CPT-11/5-FU/LV in clinical practice has not been associated with obvious safety concerns

Tandem. *Oncology Drug Use Survey.* 2001.

Post-Approval Cooperative Group Trials

Treatment Arms
(NCCTG -- Metastatic Study N9741)



Metastatic Disease

Saltz Regimen*

CPT-11: 125 mg/m²/wk x 4 wks, q 6 wks
5FU: 500 mg/m²/wk x 4 wks, q 6 wks
LV: 20 mg/m²/wk x 4 wks, q 6 wks

FOLFOX-4 Regimen†

Oxaliplatin: 85 mg/m² d1 q 2 wks
5-FU: 400 IV/600 CI mg/m² d1, 2 q 2 wks
LV: 200 mg/m² d1, 2 q 2 wks

Wasserman Regimen‡

CPT-11: 200 mg/m² d1 q 3 wks
Oxaliplatin: 85 mg/m² d1 q 3 wks

*Saltz *et al*. *J Clin Oncol* 14:2959, 1996.
†André *et al*. J Clin Oncol 17:3560, 1999.
‡Wasserman *et al*. J Clin Oncol 17:1751, 1999.

NCCTG Rapid Reporting System

- Recently implemented system for real-time reporting of adverse events
- Evaluated new mortality statistic
  - *ALL* deaths of *ANY* cause occurring within 60 days from *START* of therapy

Sargent et al. *J Natl Cancer Inst* 92:1011-1013, 2000.

Sixty-Day, All-Cause Mortality
(Metastatic Study N9741)

	Control Arm	Experimental Arms	
	Saltz CPT-11 5-FU/LV N=289	FOLFOX-4 Oxaliplatin 5-FU/LV N=277	Wasserman CPT-11 Oxaliplatin N=275
Mortality, %	4.5	1.8	1.8

Comparison between the arms was not meaningful because the therapeutic benefit of the experimental arms had not been established

Mortality Contrast
(Metastatic Study N9741 vs Study 0038)

	Study N9741	Study 0038	
	Saltz CPT-11 5-FU/LV N=289	Saltz CPT-11 5-FU/LV N=225	Mayo Clinic 5-FU/LV N=219
Mortality, %	4.5	0.9	1.4

Deaths of *ANY CAUSE* within 60 days from *START* of therapy

DRUG-RELATED deaths within 30 days from *END* of therapy

Mortality Contrast
(Metastatic Study N9741 vs Study 0038)

	Study N9741	Study 0038	
	Saltz CPT-11 5-FU/LV N=289	Saltz CPT-11 5-FU/LV N=225	Mayo Clinic 5-FU/LV N=219
Mortality, %	4.5	6.7	7.3

Deaths of *ANY CAUSE* within 60 days from *START* of therapy

Deaths of *ANY CAUSE* within 60 days from *START* of therapy

Mortality Contrast
(Metastatic Study N9741 vs Study 0038)

	Study N9741	Study 0038	
	Saltz CPT-11 5-FU/LV N=289	Saltz CPT-11 5-FU/LV N=225	Mayo Clinic 5-FU/LV N=219
Mortality, %	4.5	6.7	7.3

Sixty-day, all-cause mortality was actually *LOWER* in the post-approval N9741 trial than in the Study 0038 registration trial

Treatment Arms
(CALGB -- Adjuvant Study C89803)

Stage III Disease

RANDOMIZATION

N=635

Saltz Regimen

CPT-11: 125 mg/m²/wk x 4 wks, q 6 wks
5FU: 500 mg/m²/wk x 4 wks, q 6 wks
LV: 20 mg/m²/wk x 4 wks, q 6 wks
x 5 cycles
(30 wks of therapy)

N=628

Roswell Park Regimen

5-FU: 500 mg/m²/wk x 6 wks, q 8 wks
LV: 500 mg/m²/wk x 6 wks, q 8 wks
x 4 cycles
(32 wks of therapy)

*Saltz *et al. J Clin Oncol* 14:2959, 1996.
†Petrelli *et al. J Clin Oncol* 7:1419, 1989.

Sixty-Day, All-Cause Mortality
(Adjuvant Study C89803)

	Saltz CPT-11 5-FU/LV N=635	Roswell Park 5-FU/LV N=628
Mortality, %	2.5	1.0

Sixty-Day, All-Cause Mortality

Critical Questions

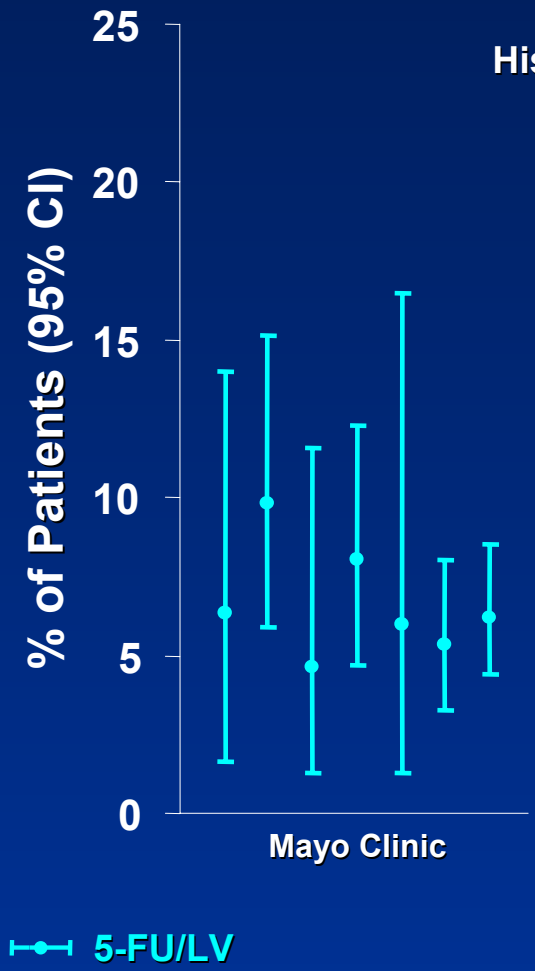
- What have these rates been historically with 5-FU/LV?
- What are the current rates in CPT-11/5-FU/LV studies?
- What are these rates with CPT-11/5-FU/LV in practice?

Overview of 60-Day, All-Cause Mortality in Colorectal Cancer Therapy

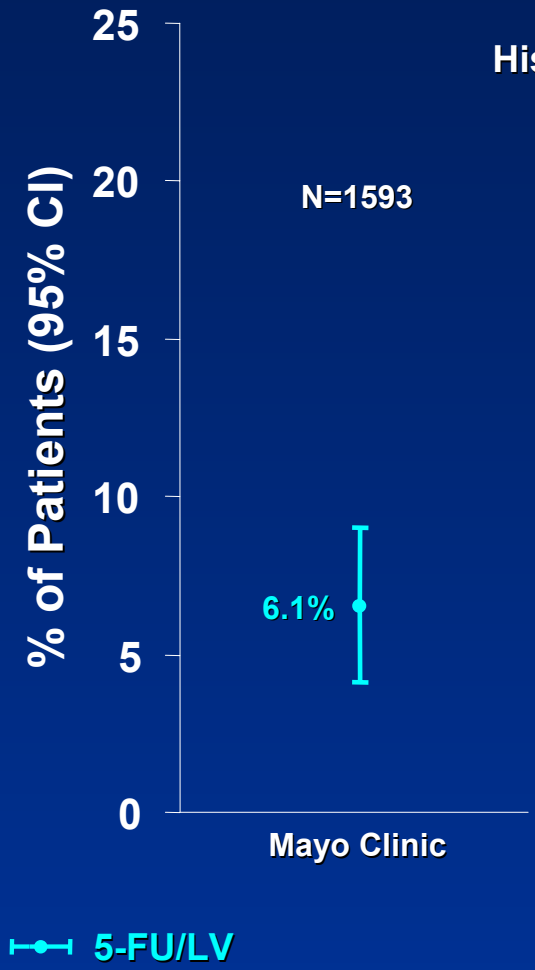
Overview Methods

- Search criteria
  - Therapy of metastatic colorectal cancer
  - Randomized, multicenter phase II or phase III designs
  - 60-day, all-cause mortality data available
- Regimens
  - 5-FU/LV: Mayo Clinic, Roswell Park, de Gramont
  - CPT-11/5-FU/LV: Saltz, Douillard
- Results
  - US cooperative groups (ECOG, NCCTG, SWOG, CALGB)
  - European cooperative groups (French and German Study Groups)
  - Industry-sponsored (Aventis, BMS, Genentech, Roche, Sugen)

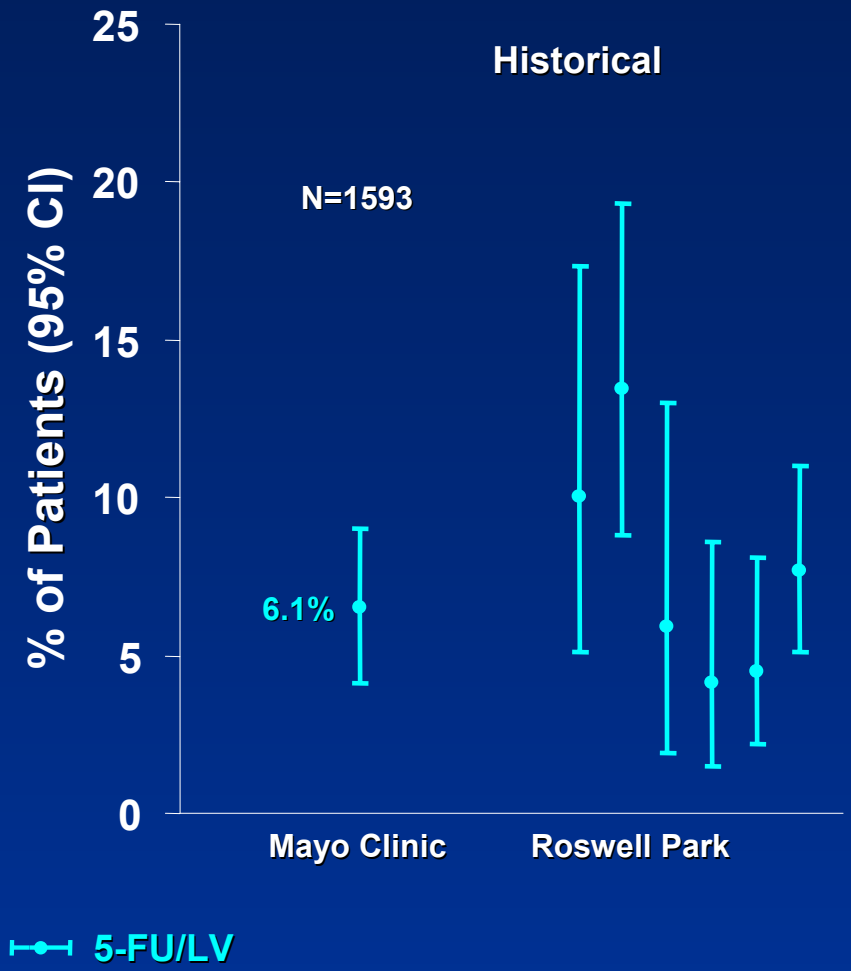
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



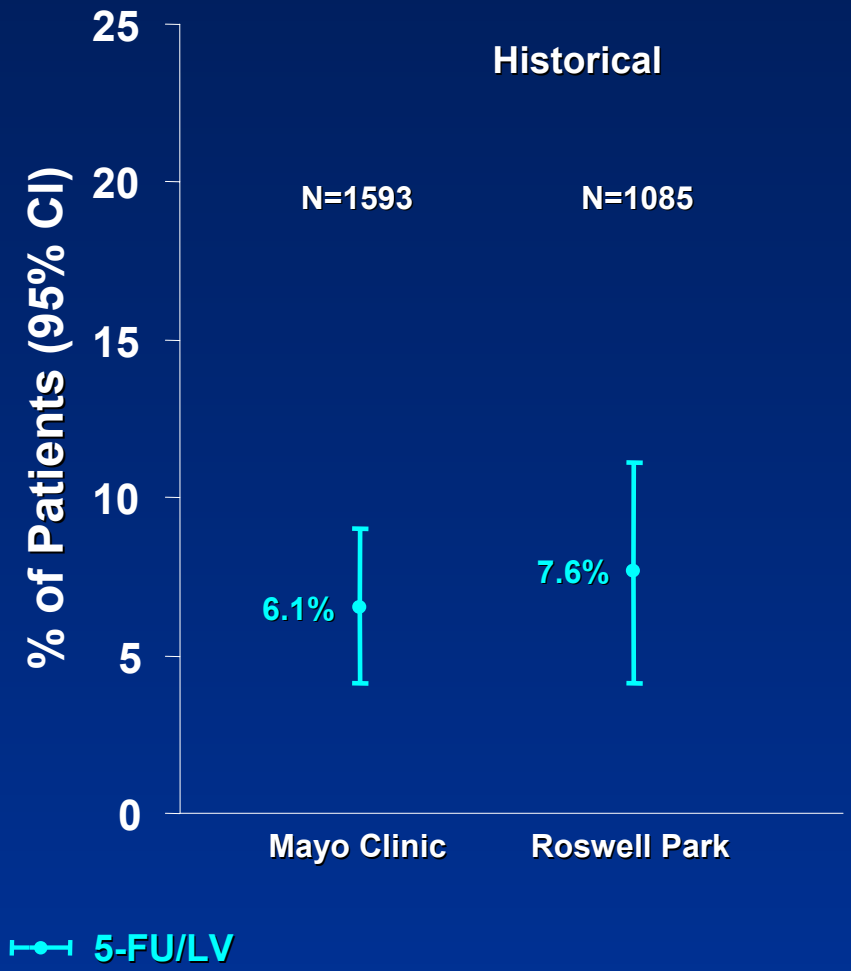
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



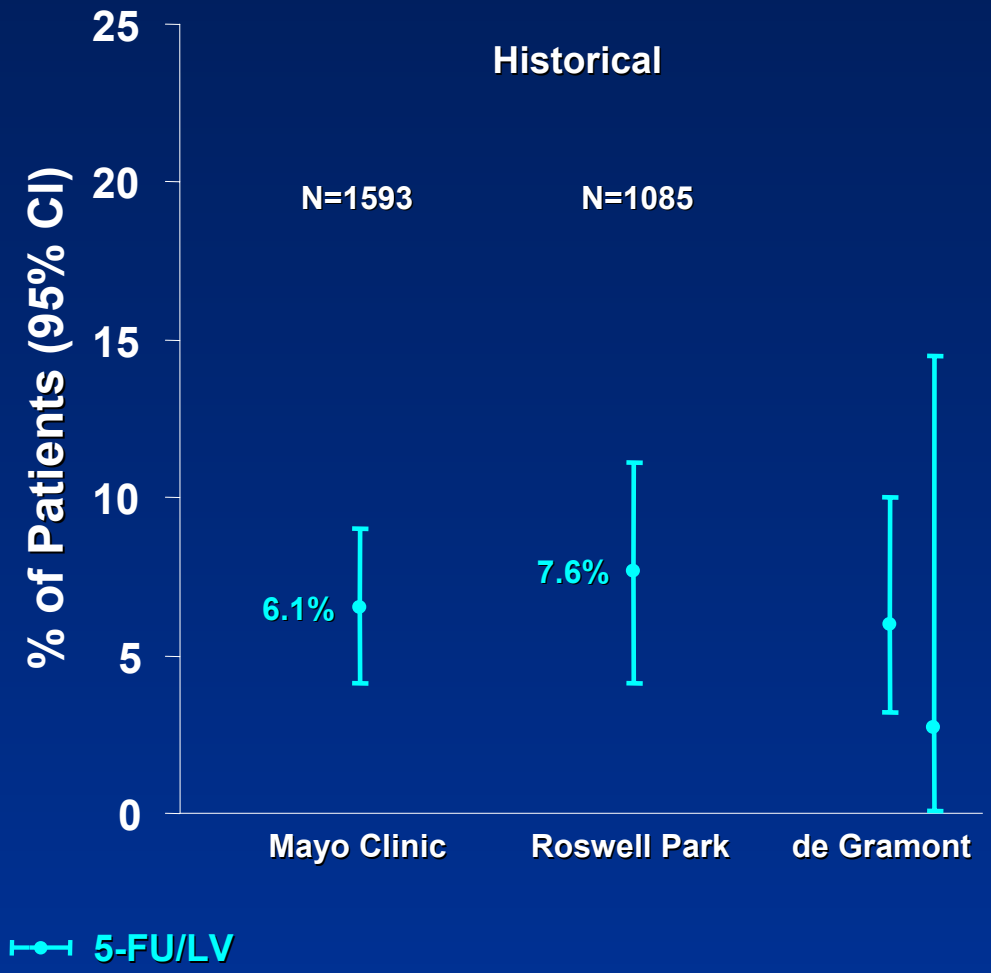
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



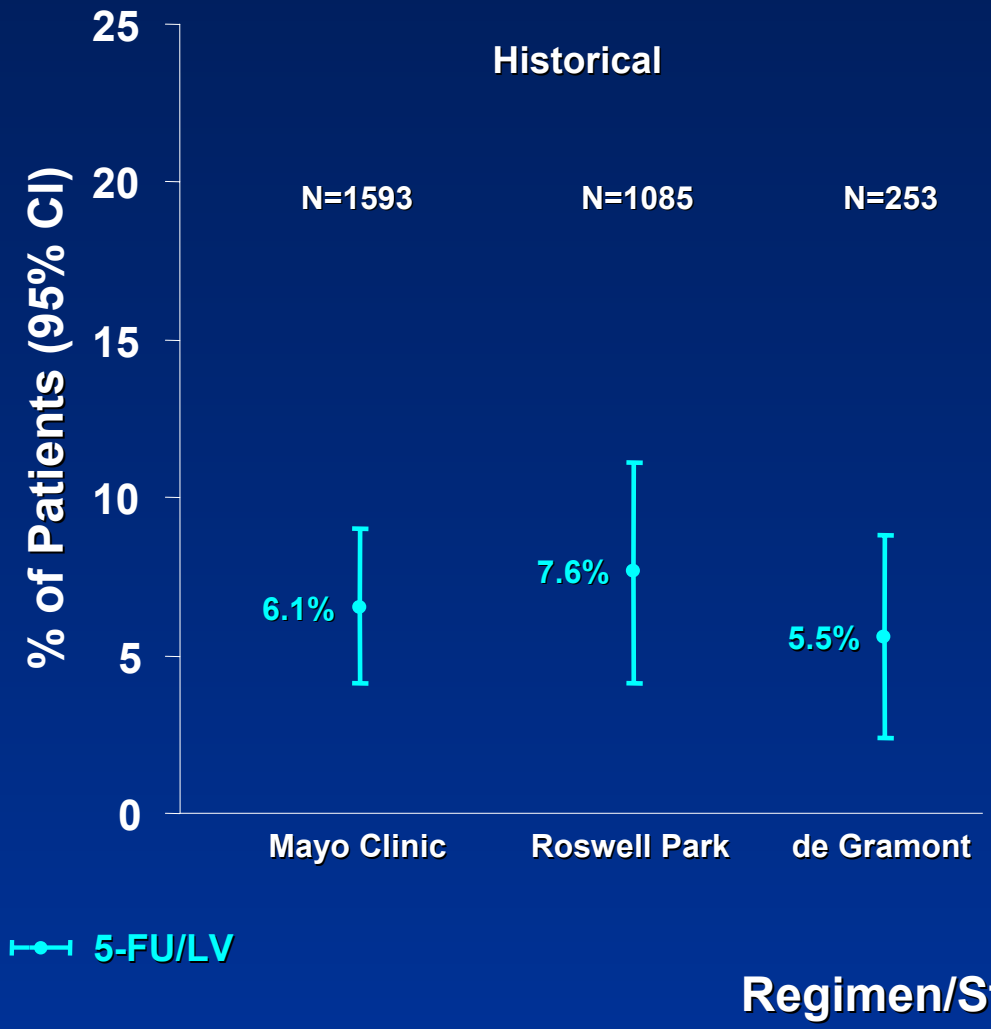
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



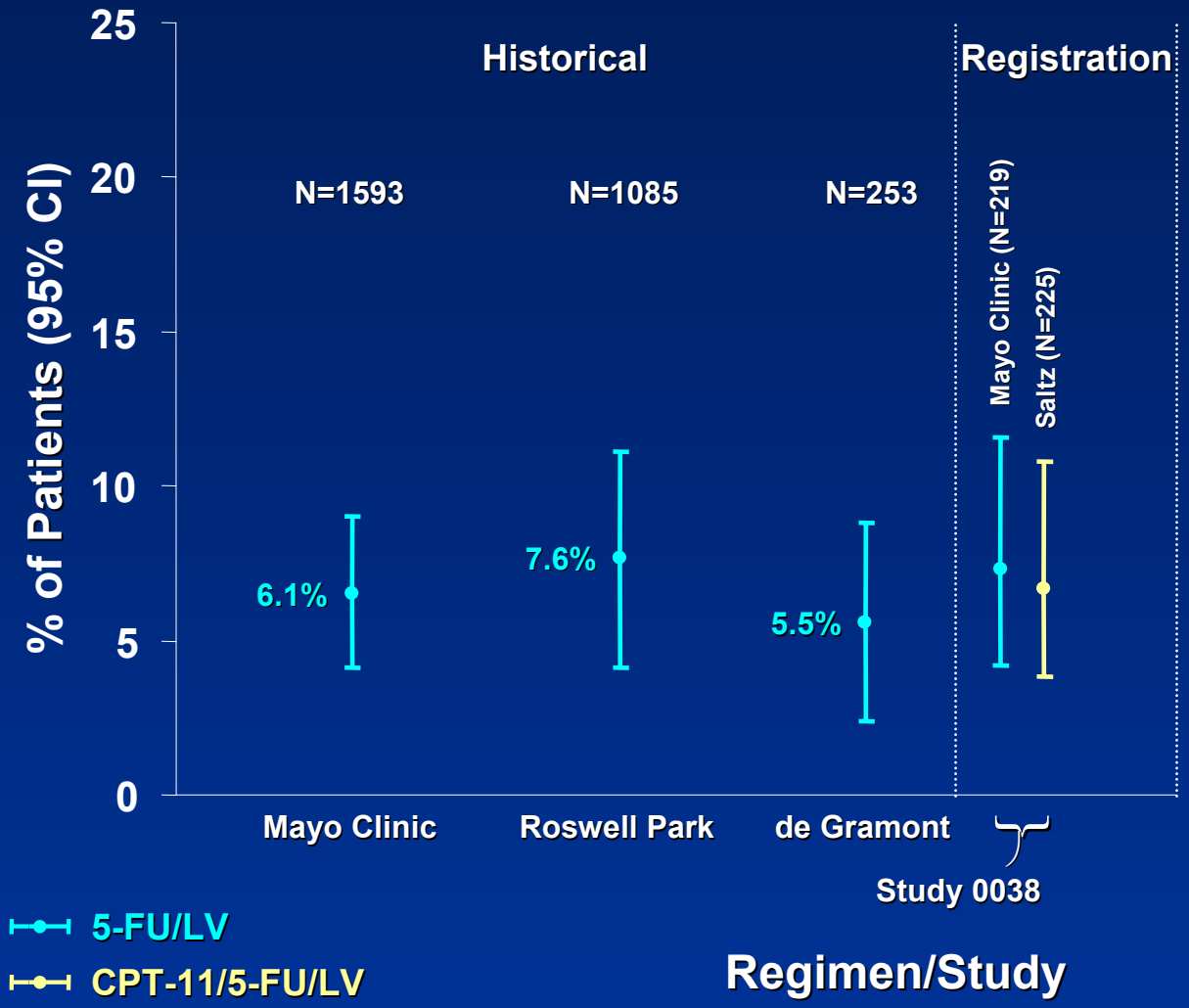
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



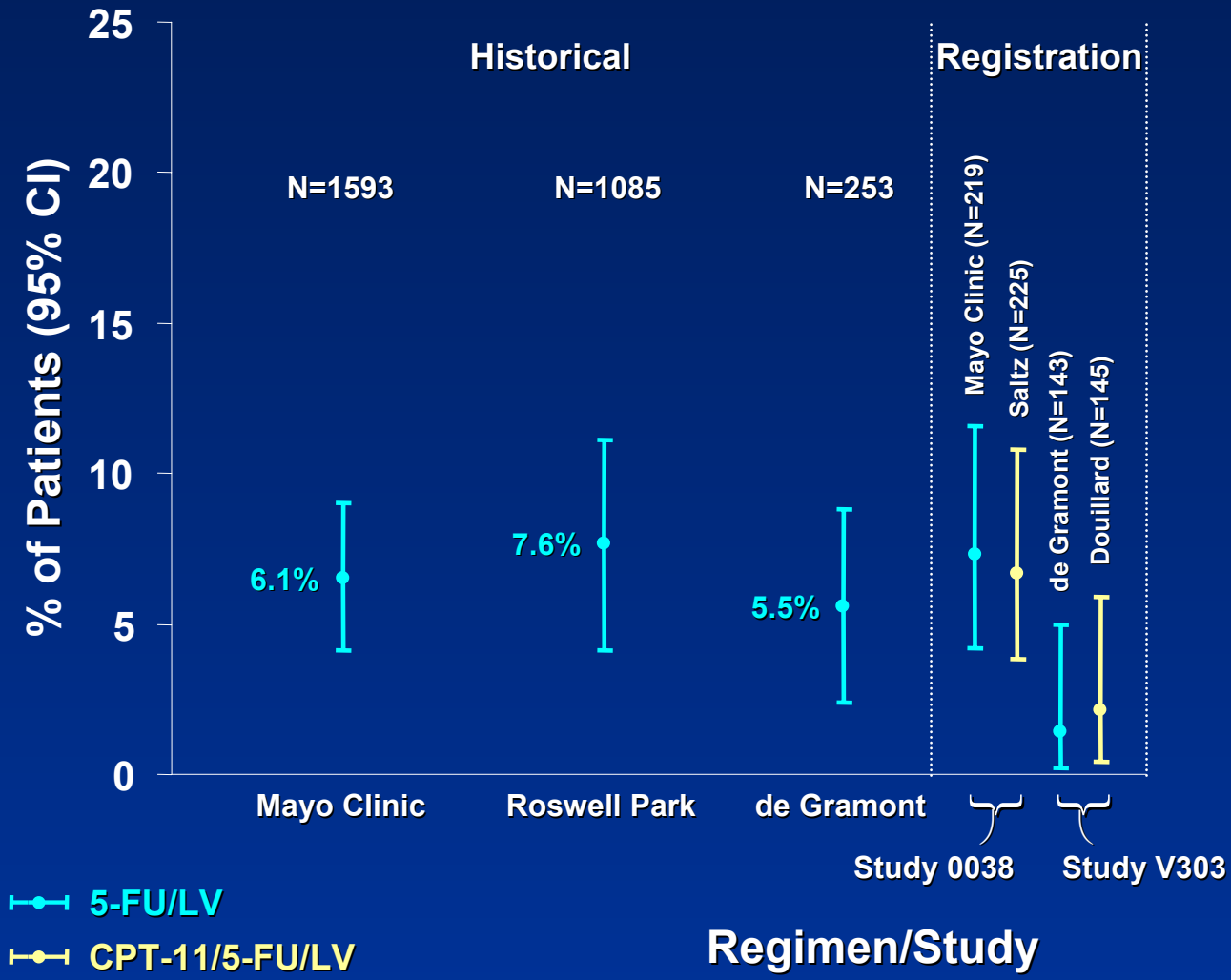
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



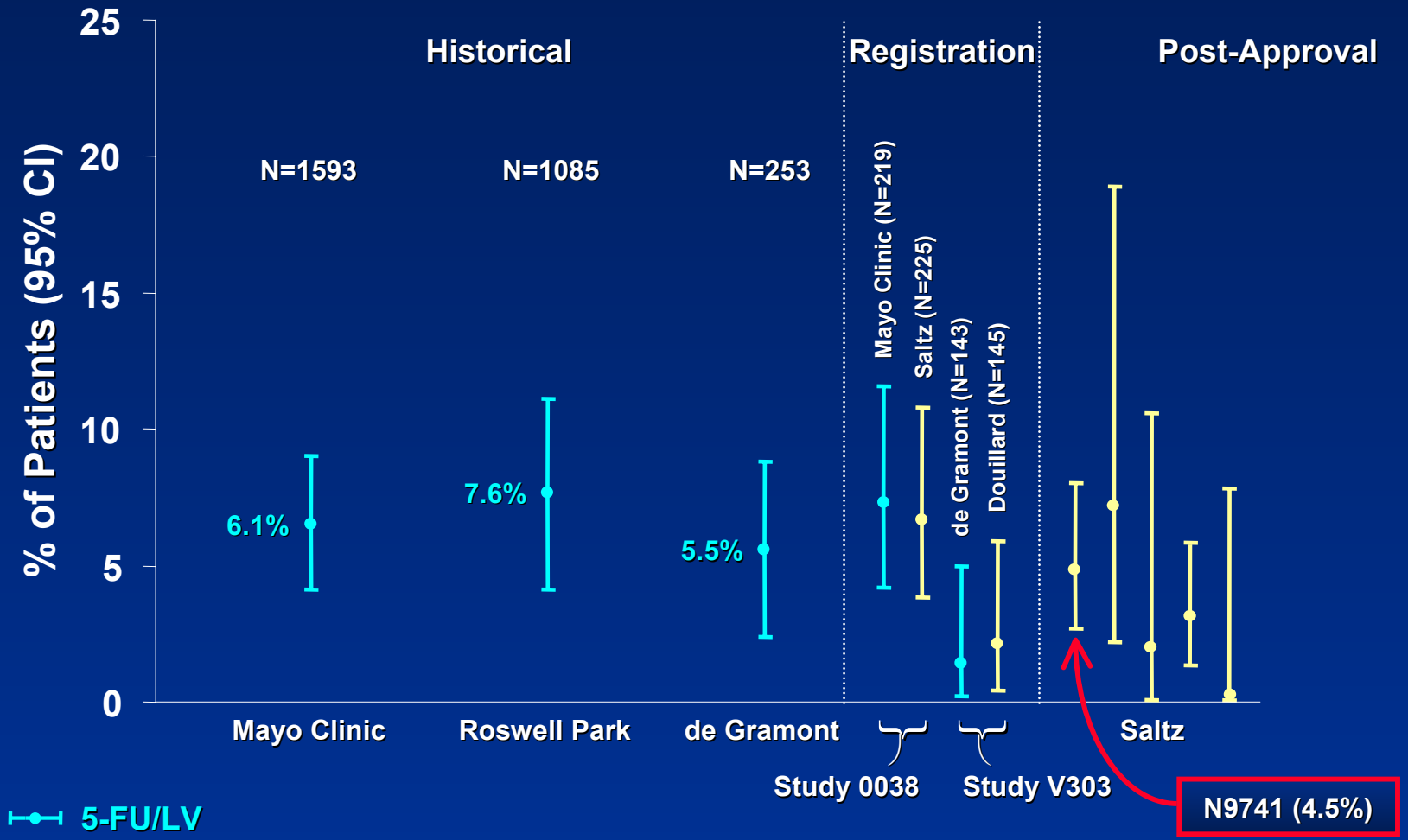
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



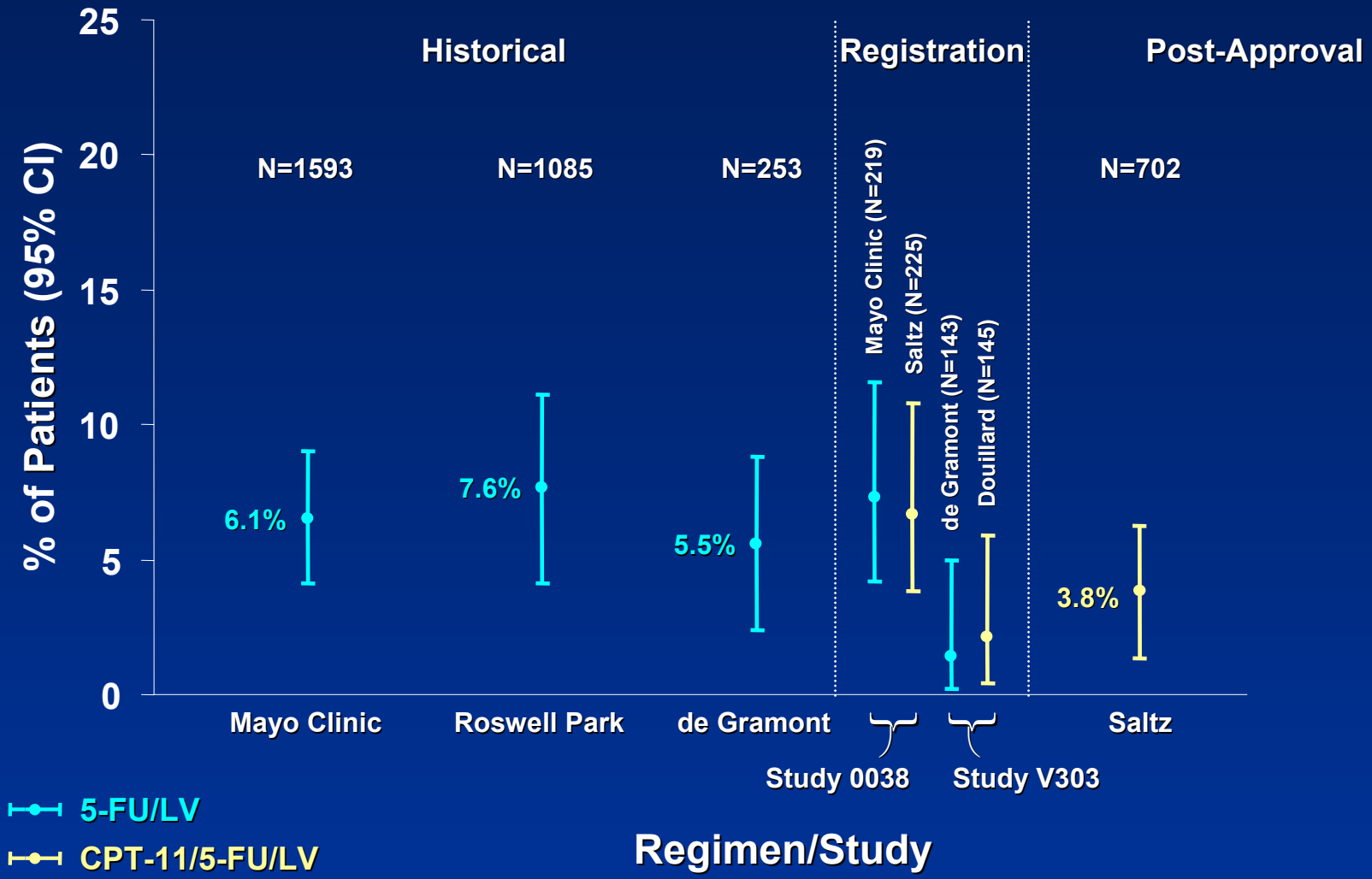
60-Day, All-Cause Mortality Rates
(Metastatic Studies)



60-Day, All-Cause Mortality Rates
(Metastatic Studies)



60-Day, All-Cause Mortality Rates
(Metastatic Studies)



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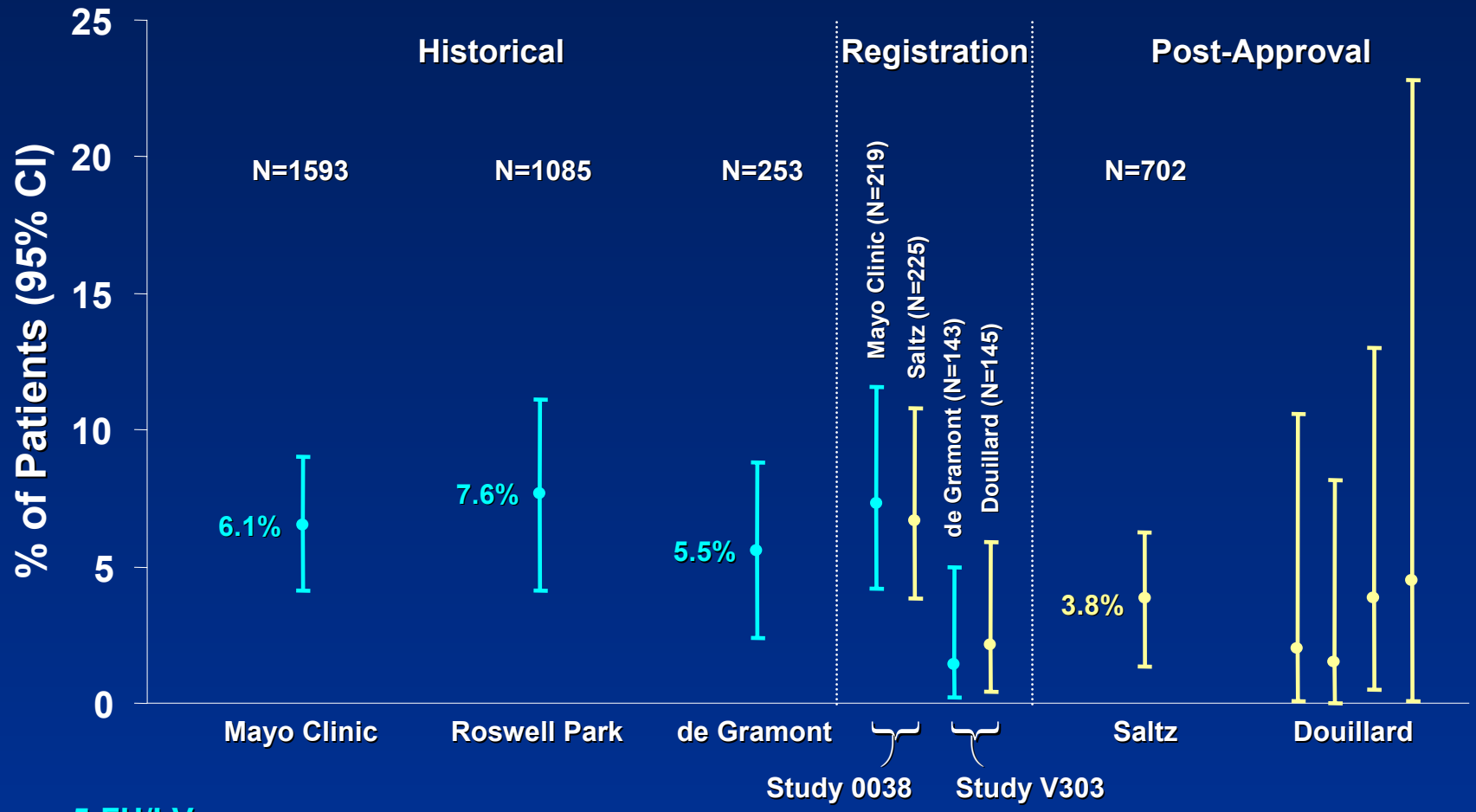

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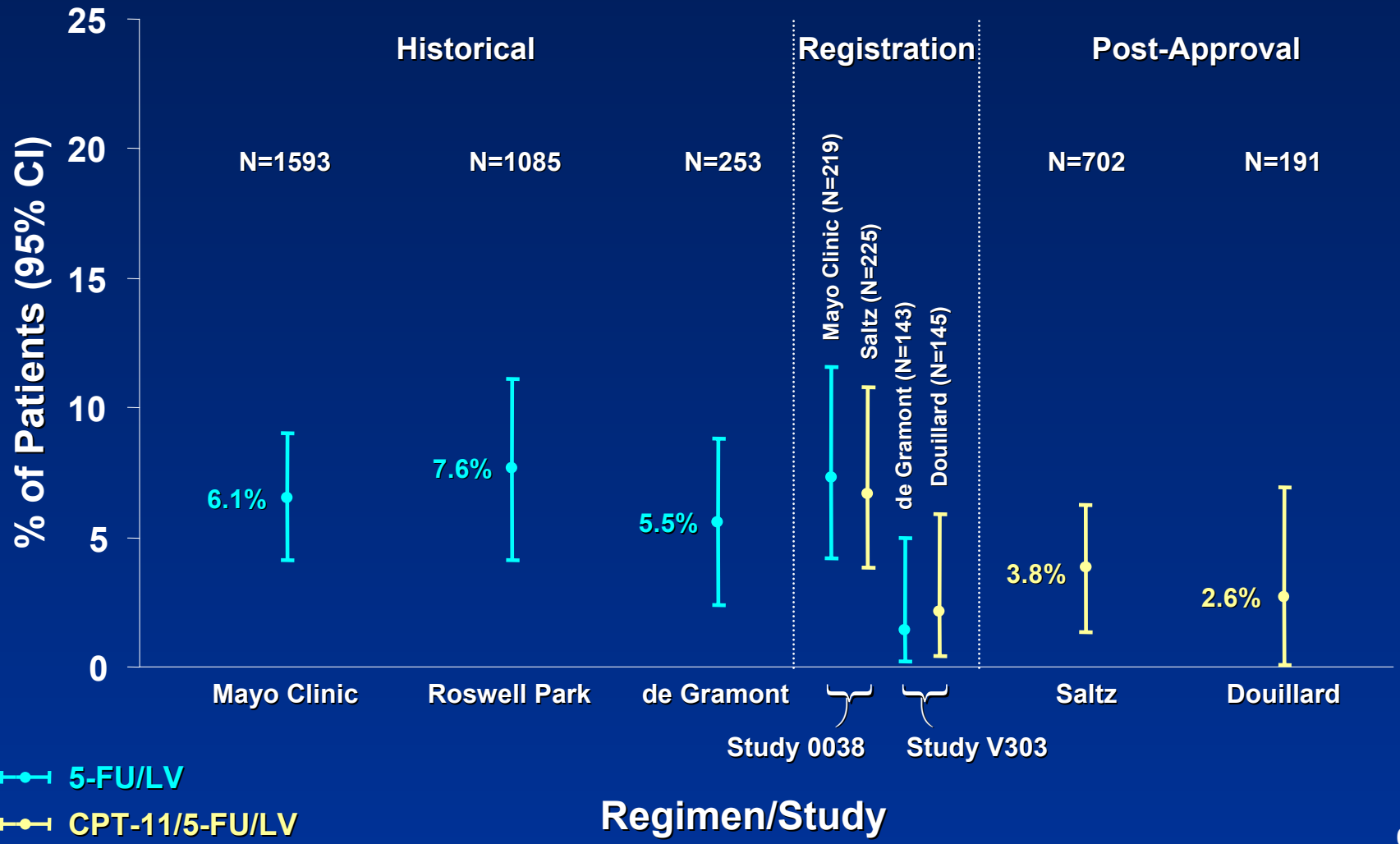


Mortality Review Summary

CPT-11/5-FU/LV
(Bolus and Infusional Regimens)

- Mortality rates are as low as with bolus or infusional 5-FU/LV regimens widely used in the past

Review of Experience with CPT-11/5-FU/LV for Metastatic Disease in Community Practice

Chart Survey Methods

- Representative mix of practice sites
  - Private practice clinics, HMOs, VA hospitals, academic centers
  - Total of 46 centers in 20 states
- Charts surveyed
  - Patients starting CPT-11/5-FU/LV between Jan 1 and April 1, 2001
  - Charts surveyed sequentially
  - Median 4 (range 1-10) patients per center
- Data collected
  - Baseline characteristics (gender, age, PS, organ dysfunction)
  - First-cycle CPT-11 and 5-FU doses
  - Death within 60 days of therapy start

Patient Characteristics
(Practice Setting, Study 0038)

Characteristic	Practice CPT-11/5-FU/LV N=240	Study 0038 CPT-11/5-FU/LV N=225
Median (range), years	61 (33-81)	62 (25-85)
Gender, %		
Males	61	65
Females	39	35
Performance status, %		
0	28	39
1	49	47
2	20	15
3	3	0
Laboratory abnormality, %		
Albumin <3.0 gm/dL	20	5
Bilirubin >2.0 mg/dL	5	<1
Creatinine >2.0 mg/dL	5	1

CPT-11 and 5-FU Starting Doses (Practice Setting)

Dose level,* mg/m²		CPT-11 N=239 % of patients	5-FU N=239 % of patients
CPT-11	5-FU		
125	500	68	72
100	400	26	24
75	300	5	3
<75	300	1	<1

*≥95% of specified dose levels

Patients Receiving Full Starting Doses (Practice Setting)

Categorization	CPT-11 N=239 % of patients
Full dose*	68
Reduced dose, reason	32
Patient compromise	25
Poor performance status	*15*
Older age	*14*
Organ dysfunction	*8*
Comorbidity	*6*
Prior pelvic radiotherapy	*4*
Physician preference	5
Other or unknown	2

* ≥95% of specified dose levels

CPT-11 First-Cycle Treatment Administration (Practice Setting and Study 0038)

Endpoint	Practice CPT-11/5-FU/LV N=240	Study 0038 CPT-11/5-FU/LV N=225
	% of patients	
Full-dose therapy*, %	44	36
4 doses administered, %	73	56
Median total dose†, mg/m^2	452	425
Mean total dose†, mg/m^2	408	412

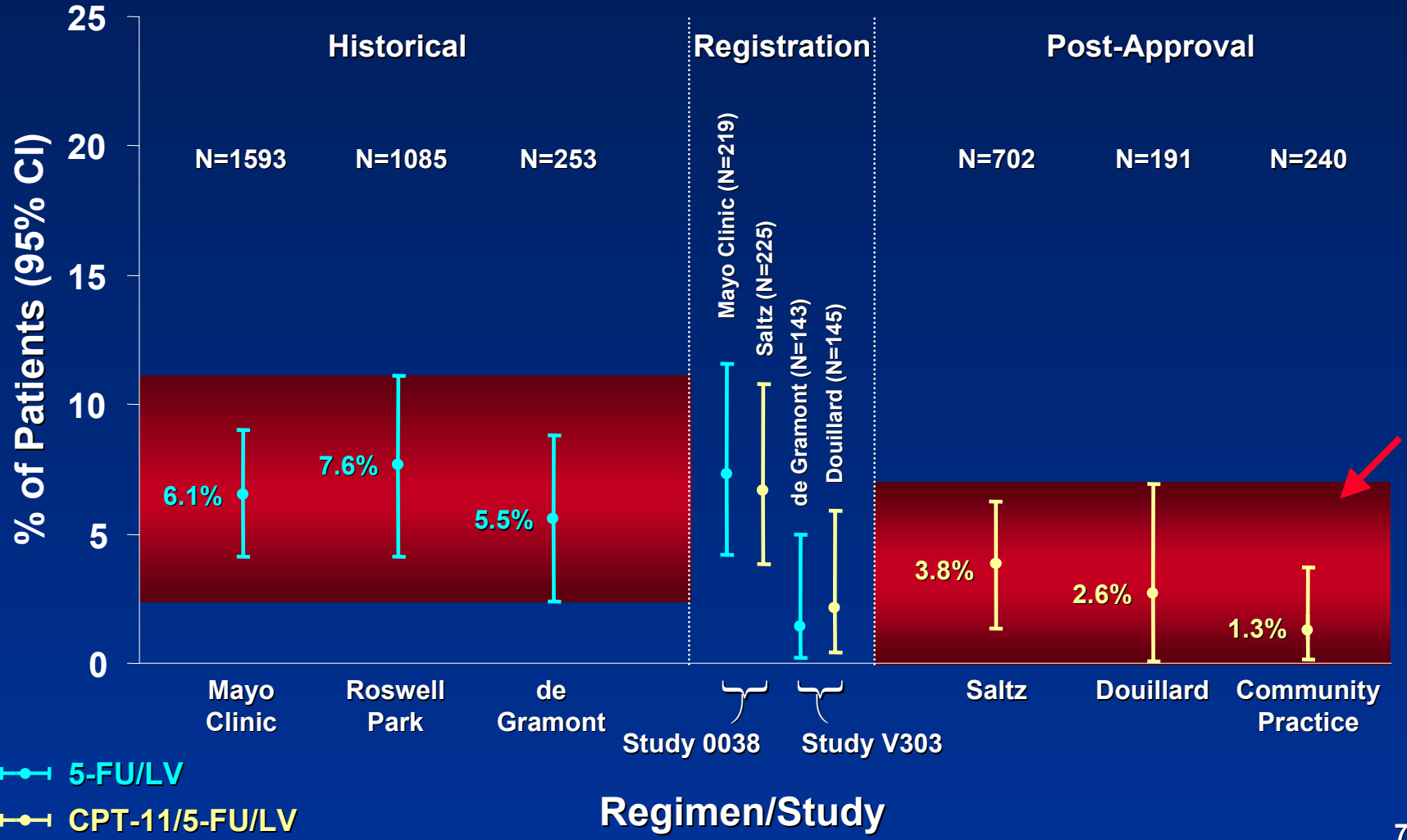
* ≥480 mg/m^2

† Sum of all therapy in first cycle

Sixty-Day, All-Cause Mortality (Practice Setting)

	CPT-11 5-FU/LV N=240
Mortality, % **[95% CI, %]**	**1.3** **0.3-3.6**

60-Day, All-Cause Mortality Rates
(Metastatic Studies and Practice Setting)



Community Practice Study

First-line Saltz Bolus CPT-11/5-FU/LV

- Administration is started at full dose whenever consistent with patient condition
- Starting dose reductions are based on clinical judgments regarding patient compromise (primarily performance status)
- First-cycle drug delivery was consistent with that observed in the registration study

Use in clinical practice is associated with a low risk of early mortality

Mortality Review and Community Practice Study

Conclusions

- Mortality rates are as low as with bolus or infusional 5-FU/LV regimens widely used in the past

Implication

- Current package insert offers sufficient guidance for safe administration

Mortality Review and Community Practice Study

Question

- Can CPT-11/5-FU/LV therapy be made even safer?

Independent Review of Deaths on N9741 and C89803

Independent Review Panel

- Coordination
  - Theradex
- Membership
  - Mace Rothenberg (Chair) -- Vanderbilt Cancer Center
  - Neal Meropol -- Fox Chase Cancer Center
  - Elizabeth Poplin -- Cancer Institute of New Jersey
  - Eric Van Cutsem -- Leuven University Hospital, Belgium
  - Scott Wadler -- Albert Einstein College of Medicine
- Dissemination
  - Rothenberg *et al*. *J Clin Oncol 19:3801, 2001.*

Independent Review Panel Findings

Conclusion

- Primary causes of early death
  - GI/hematologic cytotoxicity→sepsis
  - Vascular events

Recommendation

- Advise oncologists of the possibility of fatal GI and vascular events

Independent Review Panel Findings

Conclusion	Recommendation
♦ Primary causes of early death – GI/hematologic cytotoxicity→sepsis – Vascular events	♦ Advise oncologists of the possibility of fatal GI and vascular events
♦ Most deaths occurred in first cycle, sometimes in conjunction with infrequent monitoring	♦ Physician should see patients weekly during first cycle of therapy

Independent Review Panel Findings

Conclusion	Recommendation
♦ Primary causes of early death – GI/hematologic cytotoxicity→sepsis – Vascular events	♦ Advise oncologists of the possibility of fatal GI and vascular events
♦ Most deaths occurred in first cycle, sometimes in conjunction with infrequent monitoring	♦ Physician should see patients weekly during first cycle of therapy
♦ Antibiotic therapy not always adequate – Antibiotics given too late – Antibiotic coverage not adequate	♦ Emphasize early support with antibiotics – Oral fluoroquinolones – Broad-spectrum IV antibiotics

Independent Review Panel Findings

Conclusion	Recommendation
♦ Primary causes of early death – GI/hematologic cytotoxicity→sepsis – Vascular events	♦ Advise oncologists of the possibility of fatal GI and vascular events
♦ Most deaths occurred in first cycle, sometimes in conjunction with infrequent monitoring	♦ Physician should see patients weekly during first cycle of therapy
♦ Antibiotic therapy not always adequate – Antibiotics given too late – Antibiotic coverage not adequate	♦ Emphasize early support with antibiotics – Oral fluoroquinolones – Broad-spectrum IV antibiotics
♦ Dosing could be altered – Starting dose change not proposed – Dose modification measures should be considered	♦ Ensure a 24-hour diarrhea-free period before each chemotherapy treatment (Petrelli *et al. J Clin Oncol* 7:1419, 1989)

Independent Review Panel

Unanswered Question with Any Chemotherapy

- Are there important baseline factors that predict for early complications or death?

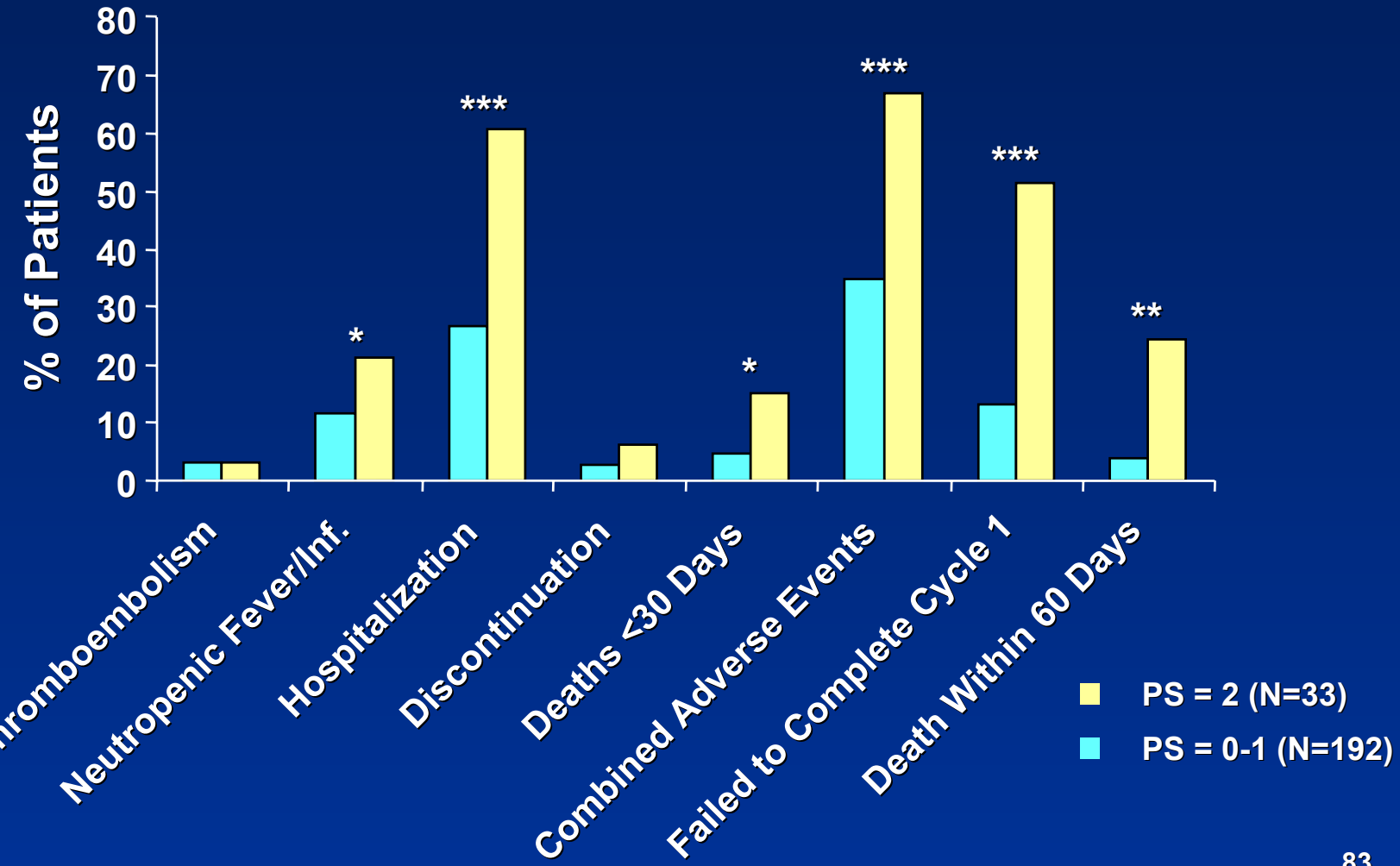
Retrospective Assessment of Risk Factors for Early Adverse Outcomes

Risk Factor Assessment Variables and Methods

- Patient characteristics
  - Age (continuous)
  - Gender (male vs female)
  - Performance status (0-1 vs 2)
  - Prior adjuvant therapy (yes vs no)
  - Prior radiation therapy (yes vs no)
  - Serum LDH (≤ULN vs >ULN)
  - Serum SGOT (≤ULN vs >ULN)
  - Serum bilirubin (≤ULN vs >ULN)
  - WBC (<8 vs ≥8 x $10^3/mm^3$)
  - Hemoglobin (<11 vs ≥11 gm/dL)
  - Creatinine (≤ULN vs >ULN)
- Adverse outcomes
  - Grade 3-4 vomiting
  - Grade 3-4 diarrhea
  - Thromboembolism
  - Grade 3-4 neutropenia
  - Grade 4 neutropenia
  - Neutropenic fever/infection
  - Hospitalization
  - Discontinuations
  - Deaths ≤30 days from last therapy
  - Combined adverse events
  - Failure to complete Cycle 1
  - 60-day, all-cause mortality

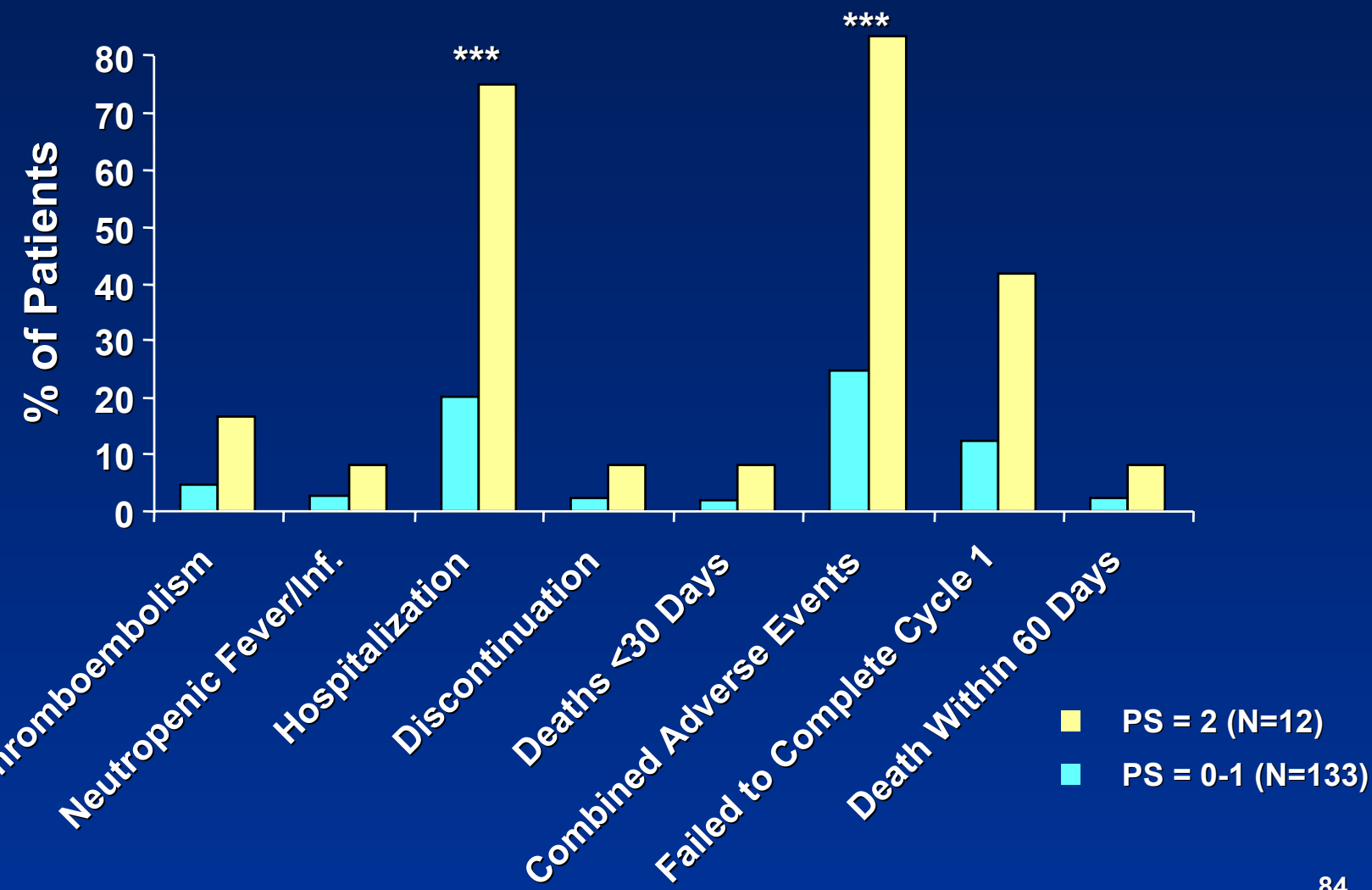
- Statistical significance was assessed by logistic regression with forward selection ($p<0.1$ for entry)

Early Adverse Outcomes by Performance Status (Saltz CPT-11/5-FU/LV -- 0038)



* p<0.05, ** p<0.01, *** p<0.001

Early Adverse Events by Performance Status (Douillard CPT-11/5-FU/LV -- V303)



*** p<0.001

Risk Factor Summary

- Performance status 2 predicted for increased risk of adverse outcomes, independent of treatment
- Performance status results corroborate findings with combination chemotherapy in other tumor types, eg,
  - Small cell lung cancer*
  - Non-small cell lung cancer†
- Other baseline factors (eg, age, gender) were not reliable predictors of adverse outcomes

* Kelly et al. Clin Cancer Res, 2001; 7:2325-2329.
† Johnson et al. *Proc Amer Soc Clin Oncol*, 1999; 18:461a [#1779].
* † Ohe et al. Proc Amer Soc Clin Oncol, 1999; 18:465a [#1795].

Overall Conclusions

CPT-11/5-FU/LV as Adjuvant Therapy Bolus and Infusional Regimens

Both Saltz and Douillard regimens

- Should remain investigational in the adjuvant setting until full benefit-risk can be determined

Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

Both Saltz and Douillard regimens

- Improve tumor control
- Prolong survival

Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

Both Saltz and Douillard regimens

- Standards of care
- Reference standards

Reverting to 5-FU/LV Alone

- Does not protect the few patients at risk of early death
- Denies tumor control and survival benefits to many patients

Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

- Do the new data demonstrate safety concerns regarding use of CPT-11/5-FU/LV for metastatic disease?

Mortality Contrast
(Metastatic Study N9741 vs Study 0038)

	Study N9741	Study 0038	
	Saltz CPT-11 5-FU/LV N=289	Saltz CPT-11 5-FU/LV N=225	Mayo Clinic 5-FU/LV N=219
Mortality, %	4.5	6.7	7.3

Sixty-day, all-cause mortality was actually *LOWER* in the post-approval N9741 trial than in the Study 0038 registration trial

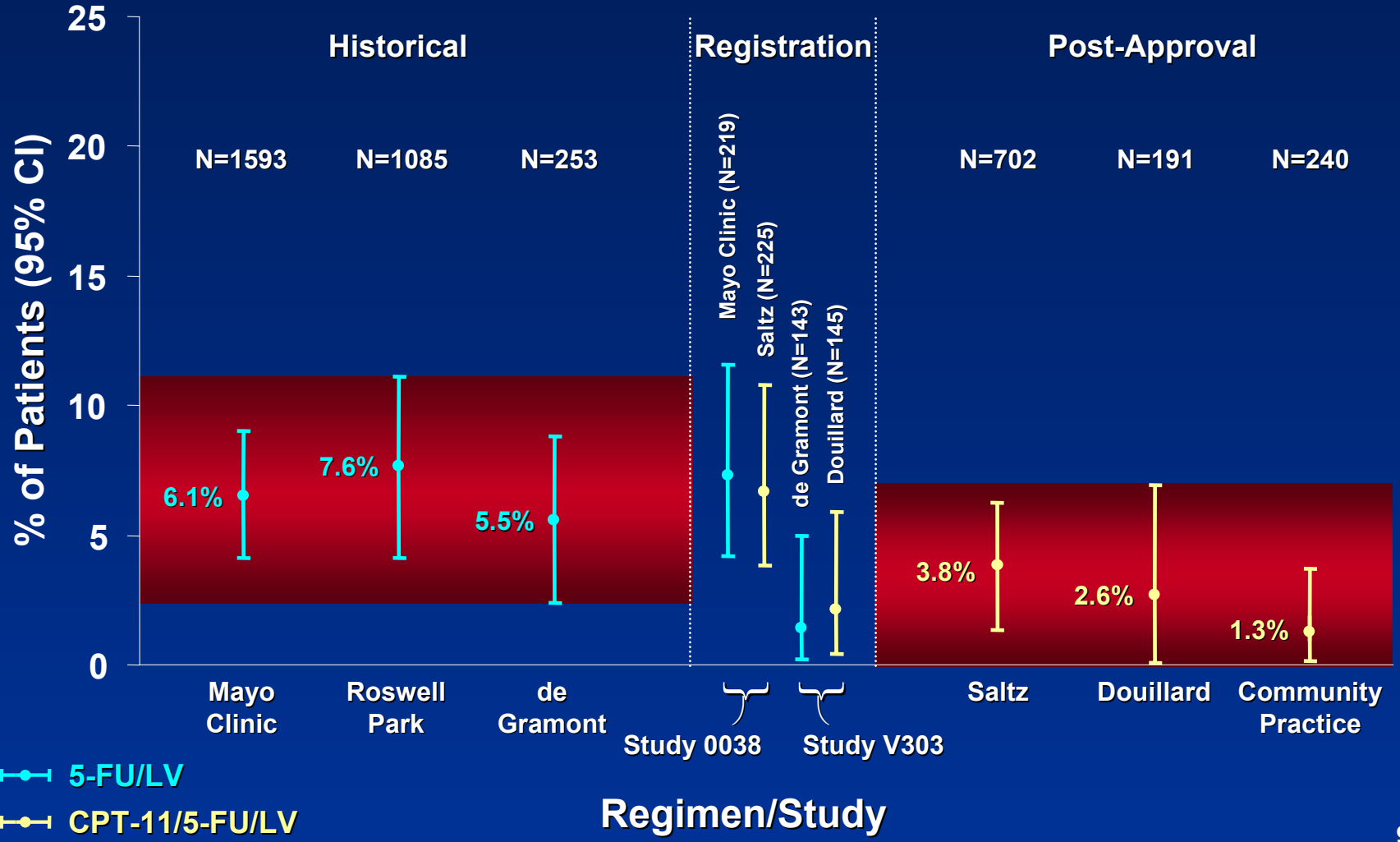
Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

- Should the CAMPTOSAR package insert be amended to include new dose modifications?

Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

- September 10, 2001 -- Proposals for package insert changes were made based on the independent panel review
- November 20, 2001 -- Pharmacia informed the FDA that new data did not support revised dose modifications

60-Day, All-Cause Mortality Rates
(Metastatic Studies and Practice Setting)



Pharmacia Recommendations Bolus and Infusional Regimens

- Current package insert offers sufficient guidance for safe administration of the regimens

Pharmacia Recommendations Bolus and Infusional Regimens

Proposed Supportive Care Changes

- Patient selection
  - Warning that patients with performance status 2 are at increased risk and that such patients should be treated only with caution and with discussion of risks
- Patient monitoring
  - Statements encouraging vigilant monitoring prior to each chemotherapy administration in first cycle
  - Documentation that thromboembolic events have occurred in the treatment of colorectal cancer
- Supportive care
  - Extension of instructions for use of oral fluoroquinolone support

Saltz Weekly Bolus Regimen
vs
Douillard Biweekly Infusional Regimen

Saltz CPT-11/5-FU/LV Bolus Regimen

- Well documented safety profile relative to former US 5-FU/LV reference standard
- *No* increase in risk of early death
  - Relative to control patients receiving 5-FU/LV
  - Relative to historical patients receiving 5-FU/LV
  - In post-approval studies (including N9741)
  - In community practice

Douillard CPT-11/5-FU/LV Infusional Regimen

- Well documented side effect profile relative to former European practice standard
- *No* increase in risk of early death
  - Relative to control patients receiving 5-FU/LV
  - Relative to historical patients receiving 5-FU/LV
  - In post-approval studies

Safety of Douillard regimen relative to Saltz regimen in US practice remains unknown

Pharmacia Recommendations

Both Saltz and Douillard regimens should be retained in the CAMPTOSAR package insert

- Safe and effective
- Greater range of disease management choices for patients and physicians
- More options in developing new drugs
- Pharmacia can continue efforts to encourage the safest use of *both* regimens in clinical practice

Statement from Ten Patient Advocacy Groups

"*We urge that the Saltz regimen be maintained so that colorectal cancer patients can continue to receive the survival benefit it offers*."

Coalition of National Cancer Cooperative Groups
Colon Cancer Alliance
Colorectal Cancer Association of Canada
Minnesota Colon and Rectal Foundation
National Colorectal Cancer Research Alliance
Interamerican College of Physicians and Surgeons
James E. Olson Foundation
Society of Gastroenterology Nurses and Associates
The Better Health Foundation
The Eric Davis Foundation

Cooperative Group Recommendations

- Michael O'Connell, MD (Chair of NCCTG and GI Intergroup)

  "*It is our opinion that it would not be appropriate to remove the (full-dose) Saltz regimen from the package insert at the present time*."
  (December 3, 2001)

- Robert Comis, MD (Chair of ECOG and Coalition of National Cancer Cooperative Groups)

  "*We believe that the Saltz regimen should continue to be available at the discretion of the treating physician*."
  (December 4, 2001)

Q & A